Clinical Development

AMN107 (Nilotinib, Tasigna®)

Protocol number CAMN107ADE20 / NCT02546674

A Phase IV single arm, multicenter, open-label study assessing deep molecular response in adult patients with newly diagnosed Philadelphia chromosome positive CML in chronic phase after two years of treatment with nilotinib 300mg BID

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Signatures of Novartis Personnel:

[redacted] signature date

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Signature of Principal Investigator (Chief Investigator according to German Drug Law):

Prof. Dr. med. [redacted]

(Principal Investigator) signature date

Signature Page for Investigator

Compound name / number Nilotinib / AMN107

Protocol number CAMN107ADE20 v03

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the principles outlined in the Declaration of Helsinki. Note: Any deviations from this protocol require a formal amendment to be approved by the responsible ethics committee.

(Investigator)	signature	date
Center name / location:		
	institution (where applicable)	city

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ABL	Abelson leukemia virus
ACE	Angiotensin-converting enzyme
AE	Adverse event
ALL	Acute lymphoid leukemia
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil count
Anti HBc	Antibody to hepatitis B core antigen
AP	Accelerated phase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AT	Angiotensin
AUC	Area under curve
BC	Blast crisis
BCR	Break point cluster region
BCR-ABL	BCR-ABL oncoprotein, BCR-ABL fusion gene, BCR-ABL fusion transcript
BID	*Bis In Die* / twice a day
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	coronary artery disease

CCyR	complete cytogenetic response
CKD	Chronic kidney disease
CML	Chronic myeloid leukemia
CP	Chronic phase
CRF	Case Report/Record Form
CPO	Country Pharma Organization
CRO	Contract Research Organization
CSR	Clinical Study Report
CVD	Cardiovascular disease
CVE	Cardiovascular event
CYP3A4	Cytochrome P450 3A4
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
ELN	European Leukemia Net
EMA	European Medicine Agency
EMR	Early molecular response
EORTC	European Organization for Research and Treatment of Cancer
ESC	European Society of Cardiology
EUTOS	European Treatment and Outcome Study for CML
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HbA1c	Glycated hemoglobin
HBs Ag	Hepatitis B surface antigen
HCT	Hydrochlorothiazide
HDL	High-density lipoprotein
HMG-CoA	3-hydroxy-3-ethylglutaryl-coenzyme A
HRQOL	Health-related quality of life

IB	Investigator brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ICVE	Ischemic cerebrovascular event
i.v.	Intravenous(ly)
IHD	Ischemic heart disease
IRB	Institutional Review Board
IS	International scale
IUD	Intrauterine device
IUS	Intrauterine system
LDL	Low-density lipoprotein
IVRS	Interactive Voice Response System
LVEF	Left ventricular ejection fraction
MR	Molecular response
MR^4	Molecular response 4 log reduction from standardized baseline
$MR^{4.5}$	Molecular response 4.5 log reduction from standardized baseline
MMR	Major molecular response
o.d.	*Omnia Die* / once a day
oGTT	Oral glucose tolerance test
PAES	Post-authorisation efficacy studies
PAOD	Peripheral artery occlusive disease
PASS	Post-authorization safety study
PCI	Percutaneous coronary intervention
PFS	Progression free survival
Ph	Philadelphia chromosome
Ph+	Philadelphia chromosome positive
PK	Pharmacokinetic
p.o.	per os / by mouth / orally
QD	Once a day
QT	QT interval

QTcF	Fridericia-corrected QT interval
Resp.	Respectively
RQ-PCR	Real-time Quantitative - Polymerase Chain Reaction
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
TdP	Torsade de pointes
TKI	Tyrosine kinase inhibitor
TFR	Treatment-free remission
SPCS	Study Protocol Concept Sheet
WOCBP	Women of child-bearing potential

Glossary of terms

MMR	≥3 log reduction from the standardized baseline or ≤ 0.1% BCR-ABL^{IS}
MR^{4}	≥4-log reduction from IRIS baseline = either (i) detectable disease ≤0.01% BCR-ABL^{IS} or (ii) undetectable disease in cDNA with 10 000–31 999 ABL1 transcripts or 24 000–76 999 GUSB transcripts.
MR$^{4.5}$	≥4.5-log reduction from IRIS baseline = either (i) detectable disease ≤ 0.0032% BCR-ABL^{IS} or (ii) undetectable disease in cDNA with 32 000–99 999 ABL1 transcripts or 77 000–239 999 GUSB transcripts.
Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study
Investigational treatment	Drug whose properties are being testing in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient number	A number assigned to each patient who enrolls in the study; when combined with the center number, a unique identifier for each patient in the study is created.
Phase	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug, combination of drugs and any control drugs including placebo
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal

Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Amendmend 3

Amendmend rational

The protocol including amendment 2 is being amended in order to correct minor issues in previous versions and clarify [redacted] prior to DBL. LPFV occurred on 20-Feb-2019.

At the time of the amendment 169 patients have been included in the trial and 21 have been ongoing.

Changes to the protocol:

Clinical Trial Team

- Changes in Clinical Trial Lead have been included

Section 10.4.3 Handling of missing values/censoring/discontinuations

- Patients who miss to have an MR assessment at 24 month, but achieved MR4.5 before will be evaluated by last available MR assessment at month 21. Overall significance level of primary endpoint is not altered.

[redacted]

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

Amendmend 2

Amendmend rational

The protocol including amendment 1 is being amended in order to add an Interim Analysis of the data to the planned procedures and to prolong the recruitment period. LPFV is planned to happen until April 30th 2019.

At the time of the amendment 53 patients have been included in the trial.

Changes to the protocol:

Clinical Trial Team

- Changes in Clinical Trial Lead and Trial Statistician have been included

Section 10.7 Interim analysis

- An interim analysis of baseline and follow-up until end of month 6 data has been added. As this analysis is purely descriptive in nature and does not include the primary endpoint, no adjustments with regards to the overall significance level will be made.

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

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Amendmend 1

Amendmend rationale

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

Changes to the protocol:

Section 1.2.2 Clinical experience

- Hepatitis B reactivation added to provide information that reactivation can occur in chronic carriers of this virus and receiving a drug of the BCR-ABL TKI class

Section 6.6.10 Hepatitis B reactivation

- This section was added to provide information on the next steps for patients tested positive for hepatitis B virus

Section 7 Table 1

- Visit schedule updated to include the hepatitis B testing at screening and once at the next possible visit when patient is on treatment

Section 7.5.5 Laboratory evaluations

- Hepatitis B serology added to provide information on hepatitis B testing

List of abbreviations was updated to add HBs Ag and anti HBc.

A copy of this amended protocol will be sent to the Ethics Committee and Health Authorities.

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatments

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of transformed, primitive hematopoietic progenitor cells. The hallmark of CML is the Philadelphia (Ph) chromosome found in up to 95% of patients. It results from a reciprocal translocation t(9;22)(q34;q11) which adds a 3' segment of the ABL gene on chromosome 9 to the 5' part of the breakpoint cluster region (BCR) gene of chromosome 22. The resulting fusion gene encodes for a constitutively active tyrosine kinase, the BCR-Abelson (ABL) tyrosine kinase (Faderl et al., 1999), which has activity that imparts growth advantage to leukemic cells, increases proliferation and cytokine-independent growth, inhibits apoptosis, and inhibits alternate adhesion pathways (Sawyers, 1999, Deininger et al., 2000, Van Etten, 2004).

With a constant incidence of 1,2-1,5/100.000 per year the prevalence of CML is steadily increasing (Hochhaus and La Rosee, 2013). Clinically, CML progresses through three distinct phases of increasing refractoriness to therapy: chronic phase (CP), accelerated phase (AP), and blast crisis (BC) (Enright H, 2000). Most patients, however, present in the CP, characterized by splenomegaly and leukocytosis with generally few symptoms.

The gold standard for the treatment of CML was the tyrosine kinase inhibitor (TKI) Glivec® (imatinib). Nilotinib (Tasigna®, AMN107) is a second generation TKI with improved target specificity over imatinib. Its efficacy and safety in the treatment of patients who are resistant / intolerant to imatinib led to its registration in second-line treatment of CP-CML and AP-CML (Kantarjian et al., 2006, Kantarjian et al., 2007, le Coutre et al., 2008). Results of the ongoing pivotal ENESTnd trial (CAMN107A2303) demonstrate a superiority of a treatment of nilotinib 300mg twice daily (BID) over imatinib 400mg once daily (QD) in newly diagnosed patients with superior rates of complete cytogenetic response CCyR), major molecular response (MMR) and deep molecular response ($MR^{4.5}$), which led to approval of nilotinib 300mg BID for the first-line treatment of patients with chronic phase CML (Larson et al., 2012).

The current European LeukemiaNet (ELN) recommendations for the management of chronic myeloid leukemia suggest continuing therapy with tyrosine kinase inhibitors (TKI) indefinitely in patients with optimal response. Nevertheless, the ELN and also NCCN guidelines highlight the possibility of treatment discontinuation for optimal responders in controlled studies, once a deep molecular response is achieved (Baccarani et al., 2013, NCCN, 2014).

1.2 Overview of nilotinib (AMN107, Tasigna®)

Nilotinib (Tasigna®, AMN107) is a rationally designed second generation TKI with improved target specificity over imatinib. Tasigna® is approved for the treatment of adult patients with Ph+ CML-CP or AP resistant to or intolerant to at least one prior therapy including imatinib, and also for the treatment of adult patients with newly diagnosed Ph+ CML in CP. Nilotinib

was also shown to be effective in patients with myeloid and lymphoid blastic phase CML (Giles et al., 2012).

Nilotinib is an adenosine triphosphate-competitive inhibitor of the tyrosine kinase activity of the native ABL as well as the chimeric fusion protein, BCR-ABL, and thereby 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 in CML (Manley et al., 2010). As well as being a highly potent and selective inhibitor of BCR-ABL, nilotinib also maintains activity against many imatinib-resistant mutant forms of BCR-ABL (Weisberg et al., 2005).

1.2.1 Non-clinical experience

Data from preclinical studies demonstrate that nilotinib achieves higher intracellular concentrations than imatinib, and that nilotinib inhibits BCR-ABL tyrosine kinase activity and induces apoptosis at lower concentrations than imatinib (le Coutre et al., 2004, White et al., 2006). Therefore, based on the preclinical data, and observed efficacy of nilotinib in imatinib resistant and intolerant patients, nilotinib was predicted to have significant efficacy in newly diagnosed CML-CP patients. For more details on non-clinical experience, please refer to the latest nilotinib IB.

1.2.2 Clinical experience

Clinical safety and tolerability

Overall, nilotinib has been found to be effective and well tolerated in patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML)-CP, and AP who were resistant to imatinib or intolerant of imatinib as well as in patients with newly diagnosed Ph+ CML-CP.

For detailed nilotinib clinical safety and tolerability, please refer to the latest nilotinib Investigator's Brochure (IB). Safety data in newly diagnosed Ph+ CML-CP have been acquired from the Phase III ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials - newly diagnosed CML-CP), [CAMN107A2303] study. Additional safety data have been acquired from a Phase I/II open-label study [CAMN107A2101] in CML patients, and a Phase III study in gastrointestinal stromal tumor (GIST) patients, as well as from further clinical studies and post-marketing experience. The most commonly reported (>5%) all grade non-hematologic adverse reactions in patients with CML were rash, headache, nausea, pruritus, alopecia, myalgia, fatigue, dry skin, arthralgia, vomiting, abdominal pain upper, muscle spasms, diarrhea, constipation, peripheral edema, dyspepsia, erythema, abdominal pain, and asthenia. Hematologic adverse drug reactions included myelosuppression (thrombocytopenia, neutropenia and anemia). Clinically relevant biochemical abnormalities included hyperglycemia, hyperbilirubinemia, hypophosphatemia, and increases in lipase, ALT, and AST. There are insufficient safety data for using nilotinib during pregnancy.

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

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

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

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

Hepatitis B reactivation

Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus and are receiving a BCR-ABL tyrosine kinase inhibitor, such as nilotinib. Some cases involving drugs of the BCR-ABL TKI class resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Clinical Efficacy

Nilotinib is approved by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) to treat newly diagnosed adult patients with Ph+ CML in CP, and to treat CP and AP Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib. The recommended adult dosage of nilotinib is 300 mg orally twice daily for newly diagnosed Ph+ CML-CP and 400 mg orally twice daily for resistant or intolerant Ph+ CML-CP and CML-AP.

The results of the pivotal ENESTnd study [CAMN107A2303] demonstrated superiority of nilotinib vs. imatinib in the CML-CP frontline setting (Saglio et al., 2010, Larson et al., 2012). This ongoing study was designed to determine whether the treatment of newly diagnosed, previously untreated Ph+ CML-CP patients, with either nilotinib 300 mg BID or 400 mg BID demonstrated improved efficacy, compared to imatinib 400 mg QD. Data cut-off for the latest, the 60-months analysis, was 30-Sep-2013. A total of 846 newly diagnosed CML-CP patients were randomized into the study. The study met its primary efficacy endpoint at the 12-month analysis time point with significantly higher MMR rates in the nilotinib arms compared to the imatinib arm (44.3% in nilotinib 300mg BID arm versus 22.3% in imatinib 400mg QD arm). By 60 months, the MMR rate remained higher in the nilotinib arms than in the imatinib arm,

indicating that the superiority of both nilotinib arms over the imatinib arm persists with longer follow-up. Furthermore, the proportions of patients achieving deep molecular response MR^4 ($BCR\text{-}ABL^{IS} \leq 0.01\%$) and $MR^{4.5}$ ($BCR\text{-}ABL^{IS} \leq 0.0032\%$) by 60 months were significantly higher in the nilotinib arms than in the imatinib arm. For more efficacy data, please refer to the latest version of the AMN107 IB.

Pharmacokinetic

Approximately 30% of a nilotinib dose is absorbed after oral administration, with peak concentrations reached at 3 hours after dosing. Plasma protein binding is high (approximately 98%) and independent of dose.

Nilotinib is metabolized in the liver via oxidation and hydroxylation pathways, mediated primarily by CYP3A4. Nilotinib was identified as the main circulating component in the serum, while none of the metabolites was found to contribute significantly to the pharmacological activity of nilotinib. In humans, excretion of nilotinib occurred exclusively through the fecal route, with no renal elimination of the drug or its metabolites observed. The average elimination half-life ($t_{1/2}$) of nilotinib is 17 hours. The bioavailability of nilotinib is increased by food: healthy volunteer studies showed increases in C_{max} and AUC (area under curve) of up to 112% and 82%, respectively (30 hours after high-fat meal, versus fasting conditions).

1.3 Overview of Molecular Response

The methodology used for identifying and quantifying BCR-ABL transcripts has evolved over the years.

A basic method for expressing results of novel and effective treatment for CML was introduced by Hughes and colleagues in 2003, who monitored the response to imatinib in previously untreated patients with CML entered in the International Randomized Study of Interferon versus STI571 (IRIS study); in order to normalize results of measuring reductions in BCR-ABL transcripts in geographically dispersed laboratories, the investigators introduced the concept of log_{10} reduction from a standardized baseline for untreated patients. At the same time, the first description of "major molecular response" (MMR) was published and defined to be a three-log reduction from the standardized baseline (Hughes et al., 2003). Three years later, the International Scale (IS) for BCR-ABL measurement was proposed. The IS further standardized the real time PCR methodology and expresses detectable disease levels as percentage with 100% IS as the standardized baseline and 0.1% IS corresponding to MMR (Hughes et al., 2006).

More recently, the terms MR^4, $MR^{4.5}$ and MR^5 have been introduced to harmonize results and to reflect the proceedings in PCR sensitivity. These values represent threshold levels for BCR-ABL transcripts at 4, 4.5 and even 5 log reductions, independent of the negativity of the PCR reaction. In relation to the International Scale, MR^4 corresponds to $\leq 0.01\%$ $BCR\text{-}ABL^{IS}$, $MR^{4.5}$ corresponds to $\leq 0.0032\%$ $BCR\text{-}ABL^{IS}$ and MR^5 corresponds to $\leq 0.001\%$ $BCR\text{-}ABL^{IS}$ (Cross et al., 2015). Unfortunately, there are still some concerns about the comparability of PCR results between different laboratories, even if these are expressed in % IS, because variations in the PCR methodology make it difficult to compare the actual results. For this reason, the European

Treatment and Outcome Study (EUTOS) group is doing an international performance evaluation with the aim of recommending specific laboratory definitions, protocols and internal quality assurance that will facilitate standardization of MR and provide greater comparability between centers (Muller et al., 2009).

Since the treatment of CML patients with especially second and third generation TKIs has proven to lead to deep molecular responses in a majority of patients (Savona, 2014), the need for accurate and standardized molecular monitoring has gained even more importance. Achieving a deeper molecular response than MMR (MR^4 or $MR^{4.5}$) is associated with a stable response after discontinuation of TKI therapy for at least a group of patients (Rousselot et al., 2007) and it is generally associated with better event-free and failure-free survival (Etienne et al., 2014). Different concepts for treatment discontinuation after achieving deep molecular responses are currently being tested in clinical trials [CAMN107I2201, CAMN107AIC05 and CAMN107A2408] and the prerequisite for entering a treatment free remission phase of these studies is the deep and stable molecular response (Cross et al., 2015).

The benefit to patients of regular molecular analysis is a reassurance of ongoing response using the most sensitive of techniques or a potential improvement in outcome for those where relapse is indicated early (Branford et al., 2007).

2 Study purpose

The therapy and management of chronic myeloid leukemia (CML) has advanced through recent years and has been revolutionized by the advent of tyrosine kinase inhibitors (TKI). TKIs transformed the status of the disease from an indolent yet progressive cancer with limited prognosis to that of a highly treatable and potentially curable cancer (Mauro, 2013, Baccarani et al., 2013).

Previous studies have shown that deeper response, particularly when attained early during treatment, is associated with better long-term clinical outcomes (Mahon and Etienne, 2014). In ENESTnd, 91% of the patients with nilotinib 300mg BID achieved a BCR-ABL level of ≤ 10% after 3 months of therapy versus 67% in the imatinib arm. Landmark analysis has shown a significantly worse PFS and OS after 5 years for patients with BCR-ABL > 10% after 3 months. In addition, significantly more patients with deep early response achieve higher rates of $MR^{4.5}$ after 5 years (Saglio 2013).

Several studies have shown that a further reduction of residual leukemic cells (i.e. achieving a deeper response compared to an MMR) is associated with the most favorable outcome for patients in CML-CP (Branford, 2008, Press et al., 2007, Kantarjian et al., 2008). In the German CML study IV life expectancy in patients with MR^4 or $MR^{4.5}$ was the same as that in an age matched population (Mahon and Etienne, 2014). No patient who has achieved $MR^{4.5}$ has progressed to advanced disease in large independent clinical trials (Hehlmann et al., 2014, Kantarjian et al., 2011, Kantarjian et al., 2012). A recent report has shown that patients who achieved a deep molecular response $MR^{4.5}$ have a statistically significant superior survival rate to that in patients with only a 2-log reduction in BCR-ABL transcript level, which has been

suggested to be the minimal molecular response equivalent of complete cytogenetic response (CCyR), (Hehlmann et al., 2014). This identifies $MR^{4.5}$ as a predictor of survival and the first molecular marker shown to be more predictive of long-term survival than CCyR (Hehlmann et al., 2014). These results provide encouraging evidence that achievement of deep molecular response $MR^{4.5}$ is an important clinical goal.

Although CML is now a chronic disease and many patients can anticipate a normal life expectancy, physicians and patients have shown a strong interest to explore treatment-free remission (TFR) strategies for BCR-ABL inhibitors. Second generation TKIs for the treatment of newly diagnosed patients have increased the proportion of patients who achieve profound molecular response and could increase the number of patients who can safely stop treatment or could discontinue treatment earlier (Breccia and Alimena, 2014, Mauro, 2013). The potential benefits of successful TFR include elimination of TKI-induced chronic and/or acute side effects, minimization of drug-drug interactions, and the possibility of a pregnancy without exposure to TKIs. Deep molecular response ($MR^{4.5}$) defines a subgroup of patients with CML who may stay in maintained remission after treatment discontinuation (Hehlmann et al., 2014).

Currently, different concepts for discontinuing treatment with TKIs are under investigation. The EURO-SKI, TIGER and ENESTpath trials are all designed for patients with a response of at least MR^4 after TKI treatment. ENESTop and ENESTfreedom however are studies for patients with a response of at least $MR^{4.5}$. To date there is no consensus about the question whether there is a difference in outcome for patients who stop treatment after a response of MR^4 or $MR^{4.5}$, therefore the proportion of patients with a response of at least MR^4 will be assessed as a secondary endpoint.

Standardized molecular monitoring has become widely available in Europe through the efforts of EUTOS cooperation (Muller et al., 2009) and now allows for the generation of comparable data on the residual disease using recalculation on the international scale despite these data being analyzed in many different laboratories. Standardization of deeper levels of molecular response is urgently needed to facilitate improved interpretation of clinical results. The ongoing EUTOS (European Treatment and Outcome Study) collaboration aims to facilitate standardization of deep molecular response across laboratories by establishing recommendations for response definitions and quality control (Mahon and Etienne, 2014).

In conclusion, nilotinib has proved superiority in reducing the leukemic burden and achieving clinical relevant parameters as well as preparing patients for TFR. The reported studies support the goal of therapy for newly diagnosed CML-CP as being an attainment of deep molecular response, as this is associated with the most favorable outcome for patients. Monitoring of molecular response provides a straightforward opportunity to assess patients' response and possible prognosis in the use of targeted therapy. Advances in the standardization of molecular responses and the improvement of targeted therapy have allowed for comparable response assessment across Europe and early treatment optimization of patients. Thus the further evaluation of deep molecular response and corresponding standardized monitoring seems justified.

The main purpose of this study is evaluating of deep molecular response ($MR^{4.5}$; $BCR\text{-}ABL^{IS}$ < 0.0032%) after 24 months of therapy with nilotinib in newly diagnosed patients with chronic phase CML. Via the use of $MR^{4.5}$ EUTOS ('European Treatment and Outcome Study for CML') laboratories adequate and reliable molecular monitoring as a key parameter for assessing molecular milestones is fostered. For definition of $MR^{4.5}$ please see section 7.4.

As modern therapy turned CML in a chronic disease where patients need to tolerate and adhere to continuing treatment for many years, assessing health-related quality of life (HRQOL) and managing side effects of TKI became a key issue for CML management (Efficace et al., 2014). The impact of TKIs on the HRQOL of CML-patients has been poorly investigated and the few studies available show that patients' HRQOL is impaired in many respects. This study will evaluate the HRQOL by using the internationally developed CML-specific QLQ-CML 24 (Efficace et al., 2014) questionnaire, which is used in conjunction with the EORTC QLQ C30 questionnaire (Aaronson et al., 1993).

In addition the study seeks to give guidance for the assessment and treatment of cardiovascular risk factors. This guidance can be applied at the discretion of the investigator based on the individual needs of the patient.

3 Objectives (and related endpoints)

3.1 Primary objective(s)

- To evaluate the proportion of patients who are in deep molecular response $MR^{4.5}$ (IS) at 24 months of study treatment, measured in a standardized EUTOS $MR^{4.5}$ laboratory.

3.2 Secondary objective(s)

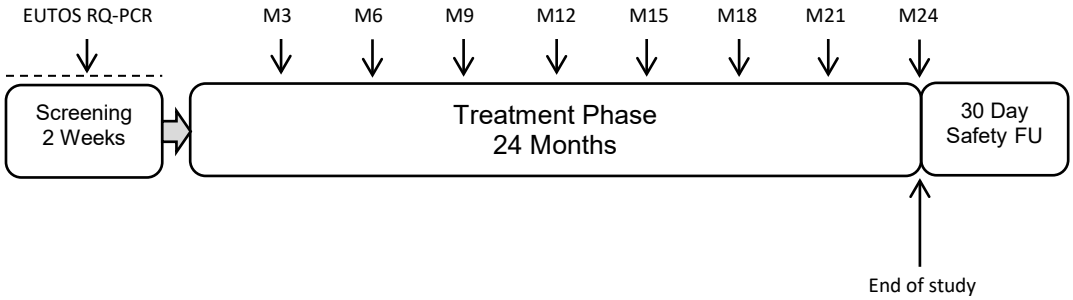
- to determine the proportion of patients who are in deep molecular response MR^{4} (IS) at 24 months of study treatment
- to determine the proportion of patients who are in MMR at 12 months of study treatment

- to determine the proportion of patients who are in CCyR at 6 months of study treatment
- to evaluate progression-free survival (PFS) and time to progression to AP/BC
- to evaluate quality of life of 300mg nilotinib BID therapy

4 Study design

This is a Phase IV open-label, multicenter, single-arm trial of nilotinib 300mg BID in newly diagnosed patients with chronic phase CML to primarily evaluate the rate of deep molecular response ($MR^{4.5}$) at 24 months of study treatment using EUTOS standardized laboratories. 171 evaluable patients will be included in at least 50 sites in Germany. All patients will receive nilotinib 300mg BID. Nilotinib will be prescribed by the investigator according to the individual needs of the patients.
A screening period of 2 weeks will be used to assess eligibility and to taper patients off disallowed medications. Patients whose eligibility is confirmed will then enter a 24 months treatment phase. The assessment to address the primary objective will be performed at the end of the treatment phase.
For efficacy analysis, only patients with typical b2a2 or b3a2 BCR-ABL transcripts at baseline will be considered. Other variants will be analyzed separately.

Table 4-1 Study outline



N = 171

5 Population

The study population will consist of a representative group of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) CML in chronic phase for who nilotinib is the appropriate treatment at the discretion of the investigator. 171 evaluable patients will be included in at least 50 sites in Germany. The decision for treatment of the patient will be made independently of the study. Prescription of nilotinib will also be independent of the study and exclusively follows the patient's medical need.

5.1 Inclusion/exclusion criteria

Patients must meet all inclusion criteria and none of the exclusion criteria to enter the study. Patients must meet all inclusion criteria within 2 weeks of study start (bone marrow examinations may be within 12 weeks). The investigative site must have all documentation of eligibility on file at the investigative site for confirmation by study monitors.

Inclusion Criteria:

1. Male or female patients at least 18 years of age
2. ECOG 0, 1, or 2.
3. Patients within 6 months of diagnosis of CML in chronic phase with cytogenetic confirmation of Ph+ [t(9;22) translocation]; if the bone marrow sample is taken within 12 weeks of the start of study treatment but before the patient consents, the bone marrow should not be repeated after the patient formally consents to the study.
4. Documented chronic phase CML will meet all the criteria defined by:
    1. < 15% blasts in peripheral blood and bone marrow,
    2. < 30% blasts plus promyelocytes in peripheral blood and bone marrow,
    3. < 20% basophils in the peripheral blood,
    4. ≥ 100 x 10^9/L (≥ 100,000/mm^3) platelets,
    5. No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly.
5. Patients must be previously untreated for CML with the exception of 6 months treatment with hydroxyurea and a maximum of 6 weeks treatment with imatinib
6. Adequate end organ function as defined by:
    - Total bilirubin < 1.5 x ULN (upper limit of normal) except know Mb. Gilbert
    - AST (SGOT), ALT (SGPT) < 3 x ULN or ≤ 5.0 x ULN if considered due to leukemia
    - Creatinine < 1.5 x ULN
    - Serum amylase and lipase ≤ 1.5 x ULN
    - Alkaline phosphatase ≤ 2.5 x ULN unless considered tumor related.

7. Normal serum levels ≥ LLN (lower limit of normal) of potassium, magnesium, total calcium corrected for serum albumin or phosphorus, or correctable to within normal limits with supplements, prior to the first dose of study medication
8. Ability to provide written informed consent prior to any study related screening procedures being performed.

Exclusion Criteria:

1. Contraindication to excipients in study medication
2. Known impaired cardiac function, including any of the following:
   - Congenital long QT syndrome or a known family history of long QT syndrome
   - History of or presence of clinically significant ventricular or atrial tachyarrhythmias
   - Clinically significant resting bradycardia (<50 beats per minute)
   - QTcF >450 msec (using the QTcF formula). If QTcF > 450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and the patient re tested for the QTc
   - History of clinically documented myocardial infarction within 12 months prior to study entry
   - History of unstable angina during the last 12 months
   - Other clinical significant heart disease (congestive heart failure)
3. History of acute (within 1 year of starting study medication) or chronic pancreatitis
4. Severe and/or uncontrolled concurrent medical conditions that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g., acute artherothrombotic events (such as ischemic heart disease, acute peripheral arterial occlusive disease, symptomatic carotid stenosis/cerebrovascular accident), uncontrolled diabetes mellitus, active or uncontrolled infections, uncontrolled severe hypertension, and uncontrolled severe dyslipidemia, acute or chronic liver or severe renal disease.
5. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug
6. History of significant congenital or acquired bleeding disorder unrelated to cancer
7. Patients actively receiving therapy with strong CYP3A4 inhibitors and/or inducers (see http://medicine.iupui.edu/clinpharm/ddis/main-table/) or medications that have the potential to prolong the QT interval (see https://www.crediblemeds.org/pdftemp/pdf/CombinedList.pdf this list may not be exhaustive) which cannot be either discontinued or switched to a different medication prior to starting study drug
8. Patients who have not recovered from prior surgery
9. Patients who are: (a) pregnant, (b) breast feeding, (c) of childbearing potential without a negative pregnancy test prior to baseline and (d) female of childbearing potential unwilling to use contraceptive precautions throughout the trial (post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential).

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 for 14 days after the final dose of nilotinib. Patients using an oral hormonal contraception method should complete their monthly treatment course. 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 (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) listed below:

  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.

10. Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively
11. Treatment with other investigational agents within 30 days of Day 1
12. Patients not able to understand and to comply with study instructions and requirements
13. Refusal to give informed consent

5.2 Premature patient withdrawal

Patients must be withdrawn from the study for any of the following reasons:

- Withdrawal of informed consent
- Pregnancy
- Study termination by the sponsor
- Disease progression (see section 6.6)
- Lost to follow up
- Death
- Permanent study drug discontinuation

Patients also should be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason. Protocol violations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

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.

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), 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.

Patients who are prematurely withdrawn from the study will not be replaced by newly enrolled patients.

6 Treatment

6.1 Patient numbering

Each patient in the study is uniquely identified by a 9 digit patient number which is a combination of his/her 4-digit center number and 5-digit subject number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 2, the third patient is assigned patient number 3). For studies using eCRFs, only the assigned patient number should be entered in the field labeled "Subject ID" on the EDC data entry screen. Once assigned to a patient, a patient number will not be reused for any other patient and the patient no. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be assigned to treatment for any reason, the reason for not being assigned to treatment will be entered on the Screening Log.

6.2 Investigational drug

Tasigna® (Nilotinib:AMN107) is the study drug.

Nilotinib will be prescribed as 150 mg hard gelatin capsule (commercial packs with blisters).

The decision for treatment of the patient will be made independently of the study. Prescription of the study drug will also be independent of the study and exclusively follows the patient's medical need.

Nilotinib will not be dosed by weight or body surface area.

6.3 Treatment arms

This is a single arm study, therefore all patients will be treated with nilotinib (AMN107) 300 mg BID, given as two 150 mg capsules twice daily.

6.4 Treatment assignment

No randomization and no IVRS/IWRS will be used in this study.

6.5 Treatment blinding

This is an open-label study.

6.6 Treating the patient

6.6.1 Dispensing the study drug

Nilotinib will be prescribed by the investigator according to the patient's medical need.

Patients will receive a prescription for the respective amount to cover the period until the next study visit or a period to be decided at the discretion of the investigator. For patients entering the study, the prescription will be dispensed on Day 1 (Visit 2). If, at the investigators discretion, it is decided to dispense the prescription drug for a shorter or longer period, then the patient must be rescheduled for an interim visit to ensure continuous medication can be given. These interim visits will not be recorded as study visits, and every attempt must be made to follow the visit schedule as stipulated in the protocol. It is recommended to prescribe a 1-month supply at Day 1 and a 3-month supply at every subsequent visit. Patients will be asked to return all unused study drug at each visit to check compliance.

6.6.2 Instructions for use of study drug

Nilotinib should be taken according to the SmPC (Summary of Product Characteristics).

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.6.3 Study drug supply and resupply, storage, and tracking

Patients will receive a prescription for the respective amount at the discretion of the investigator. The patients will get the medication at a pharmacy. The patient will be advised to present the blisters at the subsequent study visit, to review compliance and allow the investigator to complete a drug accountability check.

Storage conditions will be described in the patient leaflet (Summary of Product Characteristics).

6.6.4 Study drug compliance and accountability

Study drug compliance

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

Study drug accountability

The investigator will prescribe nilotinib in the approved indication. The patient will be advised to present the blisters at the subsequent study visits to review compliance and allow the investigator to complete a drug accountability check.

6.6.5 Disposal and destruction

n.a.

6.6.6 Permitted study drug dose adjustments and interruptions

For patients who are unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions are permitted in order to keep the patient on study drug. The following guidelines should be followed.

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

According to International Conference on Harmonization (ICH) E6 the Investigator is responsible for all trial-related medical decisions. During and following a patient's participation in a trial, the Investigator should ensure that adequate medical care is provided to a patient for any adverse events, including clinically significant laboratory values, related to the study drug. Any dose change must be recorded on the Dosage Administration Record electronic case report form (eCRF). Dose escalation is not allowed above the study dose of 300 mg BID (total 600 mg) nilotinib.

Drug adjustment should take place as soon as possible, as clinically indicated. Patients do not need to wait for a scheduled visit once clinical need has been determined. If multiple dose-reducing toxicities are present, the greatest dose reduction schedule should be used.

This study will use the CTCAE (NCI Common Terminology Criteria for Adverse Events) version 4.0 for toxicity and AE reporting. The NCI Common Toxicity Criteria version 4.0 can be downloaded from the following website: http://ctep.info.nih.gov/reporting/ctc.html. The highest reported AE grade should be used to determine the dose modification action.

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

A summary of dose reduction guidelines for study drug-related non-hematological toxicity and for ischemic vascular and cardiovascular events regardless of study drug relationship is presented in Table 6-1.

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

However, for those toxicities detailed in Table 6-1, the following rules (as detailed in the bullet points below) must be strictly followed:

- Any non-hematological toxicity Grade 3 or 4 must be resolved within 28 days to ≤ Grade 2 in order to resume study drug at the reduced dose. If a non-hematological toxicity Grade 3 or 4 does not resolve after 28 days, the patient must be discontinued from the study.
- If Grade 4 toxicity of the same type recurs despite nilotinib dose reduction to 450 mg QD the patient must be discontinued from the study.
- In case of Grade 3 pancreatitis, study drug treatment must be held and Novartis must be consulted immediately.
- In case of Grade 4 pancreatitis, study drug treatment must be permanently stopped and the patient must be discontinued from study.
- In case of Grade 4 liver toxicity, study drug treatment must be held and Novartis must be consulted immediately.
- In case of Grade 4 cardiac toxicity, study drug treatment must be permanently stopped and the patient must be discontinued from study.
- In case of recurrent QTcF prolongation to > 480 msec despite dose reduction the patient must be discontinued unless the reason for QTcF prolongation can be corrected (such as discontinuing or replacing of QT-prolonging concomitant drugs)

Table 6-1 Summary of nilotinib dose reduction guidelines for study drug-related non-hematologic toxicity and for ischemic vascular and cardiovascular events regardless of study drug relationship

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)	The dose of nilotinib may be reduced to 450 mg at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID)**
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen l→ 450 mg. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. If Grade 4 toxicity recurs despite dose reduction to 450 mg l→ discontinue from the study.
Serum hypophosphatemia	
Grade 2-3	Continue nilotinib at 300 mg BID and start phosphate supplementation.
Grade 4	Hold study drug and consult Novartis.
Serum creatinine	
Grade 2 > 1.5 -3.0 x ULN	The dose of nilotinib may be reduced to 450 mg at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.
≥ Grade 3 ≥ 3.0 x ULN	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen l→ 450 mg. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. If Grade 4 toxicity recurs despite dose reduction to 450 mg l→ discontinue from the study.
Hepato-biliary [bilirubin, AST (SGOT), ALT (SGPT)] **Note**: If hyperbilirubinemia is primarily due to the indirect bilirubin [with indirect bilirubin > direct bilirubin and direct bilirubin ≤ 1.5 x ULN and ALT ≤ Grade 1, AST ≤ Grade 1, ALP ≤ Grade 1, and hemolysis has been ruled out as per institutional guidelines (e.g. by determination of hepatoglobin)], nilotinib may be continued at the same dose, at the discretion of the investigator.	
Grade 2	The dose of nilotinib may be reduced to 450 mg at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen l→ 450 mg. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. If Grade 4 toxicity recurs despite dose reduction to 450 mg l→ discontinue from the study.
Pancreatitis (with abdominal symptoms plus lipase elevation)	

Study drug and dose	**Nilotinib 600 mg daily (as 300 mg BID)**
Grade 2	Hold study drug and perform abdominal CT with contrast to exclude pancreatic pathology. If CT is positive, continue to hold therapy and repeat CT, at investigator's discretion. If CT is negative, re-start nilotinib at 450 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 l→ discontinue from the study.
Grade 3	Hold study drug and consult Novartis.
Grade 4	Stop study drug. The patient must be discontinued from study.
Elevated lipase without symptoms	
≥ Grade 3	Hold study drug. Re-start nilotinib at 450 mg after recovery to ≤ Grade 2 is seen. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study. If toxicity recurs without symptoms consider appropriate diagnostic procedures such as abdominal CT or ultrasound to exclude pancreatitis. After recovery to ≤ Grade 2, l→ continue dosing at 450 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:	
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen l→ 450 mg. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study.
Vomiting **Note**: Antiemetic medication should be withheld until the patient experiences ≥ grade 1 vomiting then institute symptomatic therapy as appropriate. Antiemetics with the potential to prolong QT such as domperidone must be avoided. If nausea and vomiting cannot be controlled with optimal antiemetic treatment take the following actions:	
≥ Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 2 is seen l→ 450 mg. If recovery to ≤ Grade 2 is greater than 28 days, the patient must be discontinued from the study.
Skin rash **Note**: Institute symptomatic therapy as appropriate. If skin rash does not resolve with optimal treatments, take the following actions:	
Grade 2	The dose of nilotinib may be reduced to 450 mg at the discretion of the investigator if clinically appropriate and in the best overall interest of the patient.

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

Study drug and dose	Nilotinib 600 mg daily (as 300 mg BID)
Grade 2*	Hold study drug and refer patient for assessment by a vascular or cardiovascular specialist. Resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen l→ 450 mg. If another recurrence l→ discontinue from the study. If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
Grade 3* or 4*	Hold study drug and refer patient for assessment by a vascular or cardiovascular specialist. Consideration should be given for discontinuation from the study. The patient must be discontinued from the study if recovery to ≤ Grade 2 is greater than 28 days.
* Patient should be assessed for potential risk factors for the event including causality secondary to CML therapy.	
Cardiac "other"	
Grade 2 or Grade 3	Hold study drug and resume nilotinib at next lower dose level after recovery to ≤ Grade 1 is seen l→ 450 mg. 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 450 mg l→ discontinue from the study.
Grade 4	Stop study drug. The patient must be discontinued from the study.

Patients who experience Grade 2/3/4 ischemic vascular or cardiovascular events should be referred for a cardiac or cardio-vascular consult and management decisions (e.g. continue current treatment, dose reduction or study discontinuation). Patients should be assessed for potential risk factors for the event including causality secondary to CML therapy.

The SC will be informed on regular basis on the Grade 2/3/4 ischemic vascular or cardiovascular events occurring to the patients enrolled in the trial.

6.6.8 Dose reduction guidelines for study drug-related hematologic toxicity

A summary of dose reduction guidelines for ≥ Grade 3 study drug-related hematologic toxicity as determined by the Investigator is presented in Table 6-2. No dose adjustments should be made for Grade 1 or 2 hematologic toxicities. These guidelines provide some general principles as well as recommendations which are intended to support the investigator's judgment and decision about the appropriate management of toxicity in the individual patient. Please note that proceeding according to the SmPC is sufficient. However, if a hematological toxicity does not resolve to ≤ Grade 2 within 28 days, the investigator should consult with Novartis or the SC.

Table 6-2 Summary of dose reduction guidelines for study drug-related hematologic toxicity

Study drug and dose	Nilotinib 600 mg daily (as 300 mg BID)
≥ Grade 3	● Grade 3/4 1st and 2nd time: Stop nilotinib, check at least weekly, resume 600mg daily dose when Grade <3 ● Grade 3/4 3rd time: Stop nilotinib, check at least weekly, resume nilotinib at 450 mg daily dose when Grade <3 and at 600 mg daily dose after 1 week; ● Grade 3/4 4th time: Stop nilotinib, check at least weekly, resume nilotinib at 300 mg daily dose when Grade <3 and at 600 mg daily dose after 1 month; ● Grade 3/4 5th or subsequent time: Stop nilotinib until Grade <3, then contact Novartis. It will be discussed with the SC if nilotinib can be resumed or should be discontinued permanently.
Note: Dose of study drug need not be reduced or interrupted for hematological toxicity of Grade 2 or lower.	

6.6.9 Guidelines for dose re-escalation

Re-escalation of the dose of nilotinib to the 300 mg BID is permitted at the discretion of the investigator, if the following criterion is met at least one month on treatment on the reduced dose:

All ≥ Grade 3 toxicities have resolved to ≤ Grade 2

6.6.10 Hepatitis B reactivation

Patients should be tested for hepatitis B infection before initiating treatment with nilotinib as indicated in table 7.1. and section 7.5.5. Patients included before protocol amendment 1 should be tested during the study to identify patients who may be at risk for hepatitis B reactivation. Experts in liver disease should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with nilotinib should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.

6.6.11 Suggested management of cardiovascular risk factors and 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 below and in Table 6.1 (dose modifications).

The guidance provided here is not mandatory for the conduct of the study and is meant to be used as assistance at the discretion of the investigator. Assessment and management of cardiovascular risk factors is based on "The 2012 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice", the Joint ESC Guidelines, (Perk et al., 2012) and applies to all patients independently of the leukemic disease and its treatment.

Suggested management of cardiovascular risk factors

The consequent management and minimization of cardiovascular risk factors should be an important accompanying measure as the risk of cardiovascular events can possibly be reduced. Cooperation with the primary care physician and specialists (cardiologist, angiologist) is suggested, beginning from the start of the study medication. Management should be performed according to current guidelines and in regard of possible drug-drug interactions (e.g. some statins are metabolized via the CYP450 34A isoenzyme, recommendations see below).

Lifestyle factors

Basis for the minimization of cardiovascular risk are modifications of lifestyle factors.

- All smoking is a strong and independent risk factor for CVD and has to be avoided. All smokers should be given advice to quit and be offered assistance
- A healthy diet is recommended as being the cornerstone of CVD prevention
- Weight reduction in overweight and obese people is recommended as this is associated with favorable effects on blood pressure and dyslipidemia
- Patients should be encouraged for physical activity and exercise

For more in-depth information consultation of the ESC guidelines or of a cardiovascular specialist is recommended (Perk et al., 2012).

Blood pressure (BP)

Arterial hypertension is assumed when several regular measurements show systolic BP > 140 mmHg resp. diastolic BP > 90 mmHg (Mancia et al., 2013). During TKI-therapy it should be aimed for a BP < 140 mmHg systolic resp. < 90 mmHg diastolic. For patients > 80 years systolic BP < 150 mmHg is acceptable. Patients with diabetes should have a diastolic blood pressure <85 mmHg.

For patients without increased cardiovascular risk systolic BP up to 160 mmHg systolic is temporarily tolerable.

If through modification of lifestyle factors through a period of 3-6 months optimization of BP is not achieved, drug therapy is suggested with the aim of a BP systolic < 140 mmHg (Kiani et al., 2015).

For initiation of antihypertensive treatment thiazide diuretics, beta-blockers, calcium channel blockers, ACE-inhibitors or AT-receptor inhibitors are suitable, which are usually used as a monotherapy. Alternatively or if not sufficient a combination therapy can be used (Mancia et al., 2013). Please pay attention to drug-drug-interactions with the study medication; HCT, Ramipril, Lisinopril and Candesartan are examples for drugs where no interactions are to be feared (Haouala et al., 2011).

Lipids

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. Before prescribing a lipid lowering medication, the possibility of drug-drug interactions should be considered due to the moderate inhibitory effect of nilotinib on CYP3A4 isoenzyme that is involved in the metabolic pathway of some statins (HMG-CoA reductase inhibitors).

Based on the ESC guidelines (Perk et al., 2012) LDL cholesterol should be

- For very high risk patients < 70mg/dl resp. <1.8 mmol/l or at least ≤ 50% of the initial value
- for high risk patients < 100mg/dl resp. < 2.6 mmol/l
- for all other patients < 115mg/dl resp. <3.0 mmol/l

Next to dietary measures statins are used for lowering LDL-cholesterol. In regard of drug-drug interactions with the study drug pravastatin and rosuvastatin can be safely used, whereby rosuvastatin is especially recommended for high risk patients. If target-values are not achieved a combination therapy with ezetimib and statin can be considered (Haouala et al., 2011, Authors/Task Force et al., 2013, Reiner et al., 2011).

Elevated triglycerides are mostly an accompanying phenomenon of elevated cholesterol and glucose levels and should be finally assessed after optimal management of cholesterol and glucose. In this situation moderate triglyceride elevations do not necessitate intervention. For high risk patients with significant (> 500mg) elevations therapy should be considered. In this special situation in the context of interactions an expert for metabolic diseases should be consulted (Kiani et al., 2015).

Blood glucose

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.

A fasting glucose level of > 125mg/dl resp. > 7mmol/l or HbA1c value > 6.5% indicate the presence of diabetes mellitus (Authors/Task Force et al., 2013). These parameters should be assessed on a regular basis accordingly, for borderline results an oral glucose tolerance test (oGTT) can be conducted. If there are indications for a disturbed glucose tolerance or present diabetes further clarification and possibly treatment can be necessary. Consultation of a diabetologist is suggested.

Initial therapy should comprise life-style modifications and dietary measures. Regarding medical treatment interactions must be taken into account. Insulin and metformin can be safely used in this context (Haouala et al., 2011).

For patients with diabetes type 1 intensified blood glucose treatment is necessary. For patients with diabetes type 2 the HbA1c value should be ≤ 7% (Authors/Task Force et al., 2013). For patients where intensive control of glucose levels can be risky (e.g. very old age, cognitive deficits) a target value for HbA1c can be tolerated up to 7.5-8% (Stone et al., 2014). During TKI-therapy impaired glucose tolerance should be treated primarily through lifestyle modification and also by employing glucose lowering medication if lifestyle modification is not sufficient.

Platelet aggregation inhibitors

Platelet aggregation inhibitors are generally indicated for persons with cardiovascular disease in their medical history and absent contraindications. For all patients with increased cardiovascular risk the use of platelet aggregation inhibitors can be considered after individual risk-benefit evaluation. Drugs of choice are acetyl salicylic acid (ASS) with a dosage of 100mg daily or alternatively clopidogrel 75mg daily. Patients without signs for atherosclerosis and without increased cardiovascular risk should not receive platelet inhibitors (Kiani et al., 2015).

Table 6.6 Summary of recommended threshold values (details see text)

Parameter	**High & very high risk Patients**	**Moderate & low risk Patients**
Systolic BP	<140mmHg	<140(160)mmHg
Diastolic BP	<90(85)mmHg	<90mmHg
LDL	Very high risk: <70mg/dl / <1.8mmol/l High risk: <100mg/dl / <2.6mmol/l	<115mg/dl / <3.0mmol/l
HbA1C	≤7(8)%	≤7(8)%

Management of cardiovascular events

In case of occurrence of cardiovascular events (e.g. claudication, peripheral arterial disease, limp ischemia, coronary heart disease, myocardial infarction or cerebrovascular event) please refer the patient to a vascular expert. Close monitoring and minimization of risk factors will be necessary and simultaneous treatment of angiologists/cardiologists is suggested if medication is not to be discontinued.

6.6.12 Follow-up for toxicities

All patients who permanently terminate the study at any time due to a study drug related AE or abnormal laboratory value 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 (SAEs) for 30 days following premature discontinuation from any phases of the study or following end of participation as per protocol.

6.6.13 Rescue medication

n.a.

6.6.14 Other concomitant treatment

Use of the following treatments is NOT allowed after the start of study drug:

The concomitant administration of investigational drugs other than nilotinib is not allowed. The administration of any other anticancer agents including chemotherapy and biologic agents is not permitted except for anti-cancer treatments of newly diagnosed solid cancers (e.g. prostate cancer) that would not impact the level of minimal residual disease of patients. These patients may remain in study after consultation with Novartis. The administration of other tyrosine kinase inhibitors indicated for treatment of Ph+ CML is not allowed.

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

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

Every effort should be made NOT to administer a QT prolonging agent when a patient is on nilotinib treatment. If a patient is on nilotinib treatment, concomitant administration of an agent known to prolong the QT interval is required and cannot be switched to an alternative therapy, nilotinib must be STOPPED. Please see for a list of agents that prolong the QT interval at
https://www.crediblemeds.org/pdftemp/pdf/CombinedList.pdf
Please be aware that this list may not be exhaustive. In case of doubt, please consult the clinical trial team and the SmPC. Concomittant medication with “conditional risk of TdP” (Torsade de pointes) is contraindicated in case of possible interactions with nilotinib.

Cardiac monitoring is required upon re-initiation of nilotinib therapy if either study drug is stopped due to administration of any of the above medications (agents known to prolong the QT interval or strong CYP3A4 inhibitors). An ECG must be obtained both 24 to 48 hours and one week after re-initiation of nilotinib therapy. A minimum washout period of 72 hours or longer is required (depending on the half-life of the CYP3A4 inhibitor or QT interval prolonging agent) prior to study drug re-initiation.

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

Concomitant therapy requiring caution and/or action:

Cytochrome P450 3A4 substrates

Nilotinib is a moderate CYP3A4 inhibitor *in vivo*. Because of the potential risk for drug-drug interactions, the systemic exposure of other drugs known to be sensitive substrates of CYP3A4 and also to have a narrow therapeutic index should be used with caution. A list of these drugs is listed in Appendix 2 via link.

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.

Permitted concomitant therapy:

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate case report form, including the medication's duration (start and end dates or if continuing at final visit). These include blood and platelet transfusions for patients with anemia and with thrombocytopenia.

The routine use of systemic corticosteroid therapy, except dexamethasone (as it is a strong CYP3A4 inducer), is permitted.

The use of prophylactic medication for vomiting is not recommended; however, antiemetic medication can be used as clinically indicated or in the patient's best interest.

The use of loperamide may be initiated for patients experiencing ≥ Grade 2 diarrhea, before dose interruption (e.g. Imodium®, with suggested dosing to start as 4 mg PO x 1, then 2 mg PO after each loose stool, up to a maximum of 16 mg/day).

The use of hormonal contraception is permitted.

Note that previously the use of therapeutic coumarin derivatives (i.e. warfarin, acenocoumarol, phenprocoumon) was not permitted while taking nilotinib but it is now allowed. There is new data demonstrating the lack of effect of nilotinib on PK and pharmacodynamics (PD) of warfarin, suggesting nilotinib does not inhibit CYP2C9 activity in human patients. These findings suggest that warfarin may be used with nilotinib concurrently if needed (Yin et al.,

2011). Low molecular weight heparin and heparin may be substituted for coumarin and other medications for anticoagulation may also be considered at the investigator's discretion.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug (e)CRF.

6.6.15 Study drug discontinuation

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant safety risk for that patient. Permanent study drug discontinuation will lead to study withdrawal, see section 5.2. For allowed temporarily study drug interruptions please refer to section 6.6.6, Table 6.1 and 6.2.

Patients who discontinue study drug 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.

6.6.16 Definition of suboptimal response and treatment failure

The management recommendations of the European LeukemiaNet (Baccarani et al., 2013) define treatment failure as no CHR and/or Ph+ > 95% at 3 months, BCR-ABL > 10% and/or Ph+ > 35% at 6 months, BCR-ABL > 1% and/or Ph+ > 0 at 12 months and then and at any time loss of CHR, loss of CCyR, loss of confirmed MMR (in 2 consecutive tests, of which one with a BCR-ABL1 transcripts level ≥1%) as well as mutations and clonal chromosome abnormalities in Ph+ cells. Warning is defined as BCR-ABL > 10% and/or Ph+ 36-95% at 3 months, BCR-ABL 1-10% and/or Ph+ 1-35% at 6 months and BCR-ABL 0.1-1% at 12 months and then and at any time clonal chromosome abnormalities in Ph negative cells.

The response can be assessed with either a molecular or a cytogenetic test, but both are recommended whenever possible. Failure means that the patient should receive a different treatment to limit the risk of progression and death. Warning implies that more frequent monitoring is required by the characteristics of the disease and the response to treatment to allow timely changes in therapy in case of failure. The conclusion of the ELN-panel is, however, that a single measurement of BCR-ABL level is not sufficient to define as failure necessitating a change of treatment, whereas 2 tests (at 3 and 6 months) and supplementary tests in between provide more support for the decision to change treatment.

6.6.17 Progression

The following events are considered disease progression

- Death due to disease under study
- Accelerated phase (AP) as defined by any of the following:

- ≥ 15% blasts in the peripheral blood or bone marrow aspirate, but < 30% blasts in both the peripheral blood and bone marrow aspirate
- ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow aspirate
- ≥ 20% basophils in the peripheral blood or bone marrow
- Thrombocytopenia (<100 x 10^9/L) that is unrelated to therapy
- Evidence of clonal evolution (with consensus of SC only)

- Blast crisis (BC) as defined by any of the following:
  - ≥ 30% blasts in peripheral blood or bone marrow aspirate
  - Appearance of extramedullary involvement other than hepatosplenomegaly proven by biopsy (i.e., chloroma).

6.6.18 Definition of intolerance

Intolerance is defined as:

- Recurrent Grade 3 or 4 AEs persisting in spite of optimal supportive care measures and necessitating discontinuation of therapy
- Grade 2 AEs related to nilotinib that persist ≥ 1 month or recurs > three times despite dose reduction or discontinuation.

6.6.19 Emergency unblinding of treatment assignment

This is an open-label study, emergency unblinding does not apply.

6.6.20 Study completion and post-study treatment

The study will be considered completed for an individual patient when he/she completes the 30-Day FU Visit. The study will be considered completed when the last evaluable patient completes the 30-Day FU Visit.

Once planned enrollment is met, patients already in screening should be offered to enter the study. As the study drug is prescribed independent of the study, it is up to the investigator and his patient to decide this.

The study can be terminated for reasons stipulated in the study contract. Should this be necessary, the patients should be contacted and scheduled for their end of treatment assessments as described in Section 7. Novartis will be responsible for informing IRBs and/or IECs of the early termination of the study.

Treatment decision following the study is at the discretion of the investigator. Patients discontinued from the study should be given the opportunity to benefit from other therapies. The investigator also must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

6.6.21 End of treatment visit, including premature withdrawal and study discontinuation visit

At the time patients discontinue from the study, including premature withdrawal for any reason, a visit should be scheduled as soon as possible, at which time all of the assessments listed for the End of Study (EOS) visit will be performed (Table 7.1). An EOS eCRF page should be completed, giving the date and reason for stopping the study period prematurely (if applicable). All relevant information that relates to the reason for discontinuation of study including contributory factors must be included on the CRF.

At a minimum, all patients who discontinue from the study, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days after a patient ends his/her participation in the study (prematurely or as per protocol). Documentation of attempts to contact the patient should be recorded in the patient record.

Patients who discontinue from the study 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.

Patients who discontinue the study due to a study drug-related AE must be followed weekly for 4 weeks, or until resolution or stabilization of the event, whichever occurs first.

6.6.22 Follow up period

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

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

Any patient who discontinues from the study prematurely will be followed for survival, antineoplastic therapies after discontinuation of study treatment and progression to AP/BC every 3 months for up to 2 years after the patient’s start in the study.

7 Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates with an “X” the visits when they are performed.

The definition of a month is a calendar month. Patient visits for all visits during the first month of the study should be completed on the designated day (with an allowed “visit window” of ± 5 days). Patients visits for all subsequent visits should be seen on the designated day (with an allowed “visit window” of ± 7 days). If a visit was not possible within the requested time frame Novartis should be informed and further procedure discussed with the steering committee.

All data obtained from the assessments listed in Table 7.1 and described in detail in the subsections below must be supported in the patient’s source documentation. Assessments that

generate data for database entry and which are recorded on eCRF are listed using the eCRF name. Assessments that are transferred to the database electronically (e.g., laboratory data) are listed by test name.

Written informed consent must be obtained before any study specific medical procedures are performed.

Table 7-1 Assessment schedule

	Screening/ Baseline (D-14 to 0)	**Day 1**	**End of month 1**	**End of month 3**	**End of month 6**	**End of month 9**	**End of month 12**	**End of month 15**	**End of month 18**	**End of month 21**	**End of month 24 / EOS**	**30-Day safety FU**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Informed consent	X											
Inclusion/exclusion criteria	X											
Demographics	X											
Relevant medical history, history of disease	X											
Prior antineoplastic therapy and medication	X											
Physical examination	X	X[3]	X	X	X	X	X	X	X	X	X	
Weight	X	X[3]	X	X	X	X	X	X	X	X	X	
Height	X											
Vital signs / heart rate / blood pressure	X	X[3]	X	X	X	X	X	X	X	X	X	
Extramedullary involvement	X	X[3]	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X										X	
Sokal and EUTOS Score at diagnosis[1]	X											
ESC score	X				X		X		X		X	
Smoking status	X				X		X		X		X	
ECG	X		X									

	Screening/ Baseline (D-14 to 0)	**Day 1**	**End of month 1**	**End of month 3**	**End of month 6**	**End of month 9**	**End of month 12**	**End of month 15**	**End of month 18**	**End of month 21**	**End of month 24 / EOS**	**30-Day safety FU**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Hematology[5]	X	X[3]	X	X	X	X	X	X	X	X	X	
Blood chemistry	X	X[3]	X	X	X	X	X	X	X	X	X	
Hepatitis B serology[6]	X[6]											
Urinalysis	X											
Serum pregnancy test (if applicable)	X	X[3]									X	
Bone marrow assessment/ Cytogenetics (until CCyR is reached)[4]	X			X	X		X		X		X	
Peripheral blood BCR-ABL PCR	X			X	X	X	X	X	X	X	X	
Mutational analysis[2]		In case of treatment failure										
QoL Questionnaire	X			X	X		X		X		X	
Nilotinib dispensing		Continuous										
Drug compliance check			X	X	X	X	X	X	X	X	X	
Adverse events	Continuous											
Concomitant Med.	Continuous											

(1) For Calculation of SOKAL and EUTOS Score at Diagnosis, spleen size is defined as maximum distance from costal margin in [cm]; Blood counts for Basophils, Eosinophils and Blasts must be expressed in % for calculation of both Scores.
(2) In the event that a patient shows treatment failure, a study visit must be performed within 4-6 weeks. If needed, an unscheduled visit may be completed. A physical examination including assessment of extramedullary involvement, body weight, vital signs (including heart rate,

blood pressure, and body temperature), and blood work will be performed. Blood samples for PCR and mutational analysis will be taken. If needed, additional bone marrow for confirmation of cytogenetic response may also be taken.

(3) These assessments should be performed only if the Day 1 visit occurred >8 days after the Screening visit.
(4) Bone marrow aspirates and/or biopsies for cytogenetics to evaluate response are strongly recommended and will be performed at 3 months, and at the end of every 6 months until CCyR is achieved, referring to the ELN Guidelines.
(5) Additional complete blood counts should be performed every 2 weeks for the first 2 months and then monthly thereafter, or as clinically indicated.
(6) Patients will be tested for hepatitis B serology at screening. Patients included before protocol amendment 1 and currently on study treatment should have testing performed at the next possible visit in order to identify chronic carriers

7.1 Information to be collected on screening failures

Only demography data and the reason for failing (screening failure log) are collected for those patients who fail to enter the treatment phase.

Potential adverse events and hospitalizations which may have occurred from time of signing informed consent/written assent until screening failure time should be documented in the patient medical records. Reporting of potential SAE during this time period should be followed as described in Part 8.2.

7.2 Patient demographics/other baseline characteristics

Screening assessments to confirm eligibility must be performed prior to the first dose of study drug, patient eligibility is to be established by confirming all inclusion/exclusion criteria. A relevant record (e.g., checklist) must be stored with the source documentation at the study site. Violation of any entry criterion excludes a subject from enrolment into the study.

The bone marrow aspirate can be done up to 12 weeks prior to first dose of study treatment. A minimum of 20 marrow cell metaphases are required for all follow-up cytogenetic evaluations but not at baseline. FISH analysis alone will not be accepted.

All further screening assessments must be performed within 2 weeks prior to first dose of study treatment. Patients with potassium, magnesium, calcium and/or phosphorus levels that are < LLN at screening, must have their levels replenished through supplementation.

A peripheral blood sample will be drawn before start of treatment and sent to the allocated central EUTOS standardized molecular laboratory for multiplex PCR analysis (transcript type analysis).

The patient's year of birth and sex will be recorded.

Relevant medical history and current medical conditions, including those symptoms related to CML, are recorded on the respective CRF until the start of the study drug.

Prior antineoplastic medications, radiotherapy, and surgeries, including surgical biopsies, will be collected as well as prior doses and duration of imatinib and hydroxyurea.

Date of initial diagnosis of CML will be collected. EUTOS and Sokal score will be calculated retrospectively from the data collected at diagnosis or at screening, if data is not available.

Physical examination including extramedullary involvement, performance status, vital signs, ECG and laboratory assessments will be performed at screening.

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions CRF. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the patient's eCRF.

7.3 Treatment exposure and compliance

Dosage administration record

Date and time of nilotinib (morning or evening doses as appropriate) dose administration/prescription will be recorded in the respective Dosage administration/prescription record and the patient diary.

Any changes in study drug dose administration including interruption or reduction in dosing due to an AE must be reflected on the Dosage administration/prescription record and the patient diary.

Concomitant medications/significant non-drug therapies

All prescription medications and over-the-counter drugs including vitamins, herbal and alternative treatments and blood transfusions taken within 30 days prior to the start of and throughout the study must be recorded on the Prior/Concomitant Medications/Non-Drug Therapies eCRF. Medication entries should include the trade name, the start and discontinuation dates and the reason for therapy.

Compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient. The patient will be advised to present the blisters at the study visits, to review compliance and allow the investigator to complete a drug accountability check. In addition, detailed information about drug intake will be captured in the patient diary.

7.4 Efficacy

7.4.1 Molecular response

Molecular response (MR) will be assessed in all patients every 3 months until the end of study visit.

At baseline, type of BCR-ABL transcripts will be determined by multiplex PCR, levels by RQ-PCR. In subsequent samples BCR-ABL transcripts will be determined by RQ-PCR testing of peripheral blood. Samples will be analyzed at the designated EUTOS reference laboratory.

MR^4 is defined in this study as:

- ≥ 4-log reduction from IRIS baseline = either (i) detectable disease ≤0.01% $BCR\text{-}ABL^{IS}$ or (ii) undetectable disease in cDNA with 10 000–31 999 ABL1 transcripts or 24 000–76 999 GUSB transcripts.

$MR^{4.5}$ is defined as:

- ≥4.5-log reduction from IRIS baseline = either (i) detectable disease ≤ 0.0032% BCR-ABL^{IS} or (ii) undetectable disease in cDNA with 32 000–99 999 ABL1 transcripts or 77 000–239 999 GUSB transcripts.

Major molecular response is defined as:

- ≥3 log reduction from the standardized baseline or ≤ 0.1% BCR-ABL^{IS}.

At baseline a 20 mL sample of peripheral blood will be taken for multiplex PCR and RQ-PCR.

In order to monitor molecular response under study treatment (and perform mutational analyses as required), 20 mL of peripheral blood will be collected at each sampling time point in all patients. The sample will be sent to the designated EUTOS $MR^{4.5}$ reference laboratory for molecular response for evaluation of BCR-ABL transcript levels by RQ-PCR.

Mutational analysis should be done in case of treatment failure or of progression to AP/BC according to the ELN recommendations (Baccarani et al., 2013) and if clinically indicated by the investigator.

Mutational analysis is also recommended for patients in a warning zone between optimal response and treatment failure (Baccarani et al., 2013).

Table 7-2 Definition of Treatment failure, see also section 6.6.15

timepoint	Response
3 months	no CHR and/or Ph+ >95%
6 months	BCR-ABL > 10% and/or Ph+ >35%
12 months	BCR-ABL > 1% and/or Ph+ > 0
Then and at any time	loss of CHR, loss of CCyR, loss of confirmed MMR* mutations and clonal chromosome abnormalities in Ph+ cells

* in 2 consecutive tests, of which one with a BCR-ABL1 transcripts level ≥1%

If patients demonstrate treatment failure, mutational analyses will be performed on the cDNA available from the RQ-PCR at the respective time point. Continued mutational analyses may be performed following relapse at a frequency of every 3 months as needed.

If a ≥ 5-fold increase in BCR-ABL transcripts from the lowest value achieved on study is identified and confirmed by duplicate analysis of the same sample and the result corresponds to loss of MMR, the result has to be further confirmed by a subsequent sample within 4-6 weeks.

Sites will use standard materials for sample collection and shipment. Collection, storage, and shipment of samples for molecular response assessment and mutational analysis will follow the standard practice of the designated EUTOS MR[4.5] laboratory.

If a suitable peripheral blood sample for RQ-PCR testing was not obtained during the normal visit schedule then a subsequent sample must be collected at an unscheduled visit within 4 weeks.

[redacted]

7.4.3 Cytogenetic response

Cytogenetic response will be assessed as the percentage of Ph+ metaphases in the bone marrow and is defined as the following (a review of a minimum of 20 metaphases is required) and will be calculated for the Ph+ population:

- Complete (CCyR) - 0% Ph+ metaphases
- Partial (PCyR) - >0 to 35% Ph+ metaphases
- Major (MCyR) - 0 to 35% Ph+ metaphases
- Minor (mCyR) - >35 to 65% Ph+ metaphases
- Minimal - >65 to 95% Ph+ metaphases
- None - >95 to 100% Ph+ metaphases

A major response (0 to 35% Ph+ metaphases) combines both complete and partial responses.

For patients who do not achieve MCyR at 6 months mutational analysis should be obtained.

Loss of complete cytogenetic response is defined as an increase in the Ph+ bone marrow cells to >0%.

7.4.4 Bone marrow analysis and cytogenetics

Bone marrow aspiration and/or biopsy and bone marrow cytogenetics to evaluate Ph+ metaphases will be performed within 12 weeks prior to the first dose of study drug. The date of diagnosis will be considered as the date of sample from which cytogenetic diagnosis for CML-CP was made. Results from a cytogenetic analysis that was done before a patient has signed informed consent can be used. Bone marrow aspirates and/or biopsies for cytogenetics to evaluate response are strongly recommended and will be performed at 3 months, and at the end of every 6 months until CCyR is achieved, referring to the ELN Guidelines (Baccarani et al., 2013).

Bone marrow aspirates with cytogenetics will also be performed at the time there is a ≥ 5-fold increase in BCR-ABL transcripts from the lowest level achieved on study by PCR in association with either not achieving MMR or confirmed loss of MMR during therapy or when there is any other clinical indication of disease progression (e.g. progression to AP/BC based on peripheral blood and/or extramedullary assessment, loss of CHR). Standard cytogenetics are to be performed locally by the site using standard methods. A minimum of 20 metaphases must be examined in each bone marrow sample (except baseline). Cytogenetics must be performed by chromosome banding analysis (CBA) of marrow cell metaphases.

Quantification of the percentage of Ph+ chromosome metaphases, number of metaphases, number positive for Ph chromosome, cellularity, and percent of blasts and promyelocytes will be recorded on the Bone Marrow CRF. These exams will be performed and analyzed locally.

If the bone marrow is of poor quality (such as a dry tap) and makes evaluation of cytogenetic response not evaluable, the bone marrow assessment should be repeated within one month.

If additional bone marrow evaluations are performed, the results should be captured on the CRF as an unscheduled visit.

7.4.5 Hematologic response

Hematologic response includes any of the following:

• Complete hematologic response.

A CHR is defined as all of the following present for ≥ 4 weeks:

- WBC count < 10 x 10^9/L
- Platelet count < 450 x 10^9/L
- No circulating peripheral blood blasts, promyelocytes, myelocytes or metamyelocytes in the peripheral blood
- The presence of less than 5% basophils in peripheral blood
- No evidence of disease-related symptoms and extramedullary disease, including spleen and liver.

Loss of CHR is defined as the appearance of any of the following in the absence of other causes:

- WBC count that rises to > 10.0 x 10^9/L in the absence of growth factor use or acute infections
- Platelet count that rises to ≥ 450 x 10^9/L
- Any palpable spleen
- Appearance of any myelocytes, metamyelocytes, or any promyelocytes or blasts in the peripheral blood

Increasing WBC count for patients not achieving a CHR is a hematologic progression defined as a doubling of WBC count at least 1 month apart with at least the second value > 20 x 10^9/L.

7.5 Safety

Safety assessments will consist of evaluating AEs and SAEs and concomitant medications/therapies used to treat them, laboratory parameters including hematology and chemistry, body weight, physical examinations, ECG monitoring and estimation, as well as monitoring of the cardiovascular risk.

7.5.1 Adverse events

For details on adverse event collection and reporting, refer to section 8.

7.5.2 Physical examination

A physical examination will be performed according to the visit schedule (refer to Table 7.1), i.e. during screening and at every visit. Information about the physical examination must be included in the source documentation at the study site and will not be recorded in the eCRF.

A complete physical examination will include the assessment of weight and an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological.

Height will be measured at screening only.

Extramedullary involvement

Presence of extra-medullary leukemic involvement will be checked with each physical examination as outlined above. Findings on physical examination consistent with extramedullary leukemic involvement will be recorded (e.g. lymph nodes, liver and spleen size). With regards to lymph nodes, only those palpable lymph nodes should be considered to be CML related if leukemic blast infiltration has been confirmed via biopsy/histology or by technically adequate (not contaminated with peripheral blood) aspiration cytology. When extra-medullary involvement other than of the spleen or liver is the only evidence of blast crisis, this finding must be confirmed by technically adequate (not contaminated with peripheral blood) aspiration cytology and /or biopsy (especially for isolated lymph nodes) and data entered into the extramedullary involvement eCRF.

7.5.3 Vital signs and weight

Vital signs and weight should be performed during screening and at every visit. Pulse rate (sitting, after two minutes of rest), blood pressure (sitting, after two minutes of rest), body temperature, and weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) as specified in Table 7-1 must be present in the patient's chart, and captured on the eCRF. Height will be measured only at screening and recorded on the eCRF.

To detect early signs of fluid retention, patients should be weighed according to the visit schedule, and should also weigh themselves regularly at home. Patients are encouraged to report to the study Investigator any body weight change of more than 2 kg as compared to their pre-study body weight. Rapid weight gain of ≥ 2 kg should be carefully investigated and other measures considered as appropriate.

7.5.4 Performance status

Performance status will be recorded in the eCRF according to Table 7-1 and as defined by the following ECOG criteria, published by the Eastern Cooperative Oncology Group (Oken et al., 1982):

Table 7-3 ECOG performance Criteria

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.5.5 Laboratory evaluations

The laboratory evaluations will be performed by a local laboratory. Novartis must be provided with a copy of the certification and tabulation of the normal ranges for all local laboratories used.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g. require dose modification and/or interruption of study drug, lead to clinical symptoms or signs

or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the appropriate comment CRF page in addition to the appropriate laboratory CRF page.

When abnormal laboratory values or test results constitute an adverse event (i.e. induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events CRF. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant (e.g. cause study discontinuation or constitutes in and of itself a Serious Adverse Event) or require therapy (e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them.

Hematology

Hematology labs are to be done locally at the site. Hematology includes assessment of hemoglobin, platelets count, total white blood cell count (WBC) and a full differential count in percentage or absolute values including neutrophils, lymphocytes, eosinophilis, basophils, monocytes, promyelocytes, myelocytes, metamyelocytes, and blast cells. In laboratories where manual differentials are not routinely performed, automated differential counts will be accepted.

Additional complete blood counts should be performed every 2 weeks for the first 2 months and then monthly thereafter, or as clinically indicated.

Biochemistry

Clinical chemistry tests will include AST (SGOT), ALT (SGPT), direct bilirubin, total bilirubin, alkaline phosphatase, lipase, amylase (optional), lactate dehydrogenase (LDH), albumin, triglycerides, high-density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol, fasting glucose, HbA1c, serum creatinine, sodium, potassium, magnesium, calcium, GFR and inorganic phosphorus. Potassium, calcium, magnesium, and/or sodium supplements may be given to correct values that are < LLN. Regarding substitution please proceed according to general standards in internal medicine. Post-correction values must not be deemed to be a clinically significant abnormality prior to patients being dosed.

Glucose, HDL, LDL, total cholesterol and triglycerides should be assessed under fasting conditions.

Hepatitis B serology

Patients will be tested at screening for the following hepatitis B serologic markers: hepatitis surface antigen (HBs Ag) and antibodies to hepatitis B core antigen (anti HBc).

Patients included before protocol amendment 1 and already on study treatment should have testing performed at the next possible visit in order to identify chronic carriers.

Urinanalysis

At Screening, a standard urine test will be performed. Additionally the presence of micro albuminuria should be tested.

7.5.6 Pregnancy test and assessments of fertility

A serum pregnancy test is mandatory at screening and at end of study or at early discontinuation visits for female patients of child-bearing potential (definition see section 5).

Pregnancy testing is not required for patients who are determined to be post-menopausal. 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) or have had surgical bilateral oophorectomy with or without hysterectomy or tubal ligation at least 6 weeks prior to enrolling. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered to be not of childbearing potential.

7.5.7 Organ-specific safety monitoring

Cardiac assessment

After the subject has rested approximately 10 minutes in a semi-supine position, a single 12-lead ECG must be obtained at the time points indicated in Table 7.1 and whenever clinically indicated at Investigator's discretion, e.g. when concomitant medication is changed.

Interpretation of all ECGs must be done by a qualified physician. Each ECG tracing should be labeled with the study number, subject number, date, and kept in the source documents at the study site. Clinically significant abnormalities present prior to the start of study drug should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after the start of study drug must be recorded on the Adverse Events eCRF page.

QTc will be calculated according to Fridericia's formula.

The patient should not be dosed if the ECG confirms a QTcF >480 ms (please refer to Table 6-1 for dose modification instructions related to QTcF prolongation) or >450 ms at screening.

In case of a grade 3 QT prolongation, a cardiologist opinion should be requested and an appropriate and closer cardiac monitoring of the patient must be put in place until the QTcF decreases to <500ms.

7.5.8 Estimation and monitoring of the cardiovascular risk

The basis for the estimation of the individual cardiovascular risk of a patient is "The 2012 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice" (Perk et al.,

2012). In these guidelines patients are divided in four risk groups: very high, high, moderate and low risk.

Part of the ESC risk estimation is calculation of the SCORE (Systematic Coronary Risk Evaluation), where through several parameters the 10-year risk of a first fatal atherosclerotic event is estimated. The SCORE can be calculated using an online calculator (http://www.heartscore.org/) or using the chart in Appendix 4. The following parameters are needed to calculate the ESC Risk-Score:

- Age
- Sex
- Systemic blood pressure
- Cholesterol [mmol/l or mg/dl]
- Smoking status

Given that some risk factors are modifiable, the SCORE will be newly calculated at baseline and every six months during the treatment.

The individual cardiovascular risk estimation for a patient is defined as follows:

1. Very high risk - Subjects with any of the following:

- Documented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound), previous myocardial infarction, ACS, coronary revascularization (PCI, CABG), and other arterial revascularization procedures, ischaemic stroke, peripheral artery disease (PAD).
- Diabetes mellitus (type 1 or type 2) with one or more CV risk factors and/or target organ damage (such as microalbuminuria: 30–300 mg/24 h).
- Severe chronic kidney disease (CKD) (GFR <30 mL/min/1.73 m^2).
- A calculated SCORE ≥10%.

2. High risk - Subjects with any of the following:

- Markedly elevated single risk factors such as familial dyslipidaemias and severe hypertension.
- Diabetes mellitus (type 1 or type 2) but without CV risk factors or target organ damage.
- Moderate chronic kidney disease (GFR 30–59 mL/min/1.73 m^2).
- A calculated SCORE of ≥5% and <10% for 10-year risk of fatal CVD.

3. Moderate risk

Subjects are considered to be at moderate risk when their SCORE is ≥1 and <5% at 10 years. Many middle-aged subjects belong to this category. This risk is further modulated by factors mentioned above.

4. Low risk

The low-risk category applies to individuals with a SCORE <1% and free of qualifiers that would put them at moderate risk.

Persons with established CVD need prompt intervention on all risk factors, while in apparently healthy persons total risk should be assessed by using the score system.

The higher the risk, the greater is the benefit from preventive efforts. Low-risk persons should be offered advice to maintain their low-risk status. While no threshold is universally applicable, the intensity of advice should increase with increasing risk. In general, those with a risk of CVD death of ≥5% qualify for intensive advice, and may benefit from drug treatment. At risk levels >10%, drug treatment is more frequently required. In persons older than 60, these thresholds should be interpreted more leniently, because their age-specific risk is normally around these levels, even when other cardiovascular risk factor levels are 'normal'.

Especially patients with increased cardiovascular risk should be under close monitoring and their risk factors should be strictly controlled. Patients in risk group 1 (very high risk) should be referred to a cardiovascular specialist. Ongoing minimization of modifiable risk factors is suggested for all patients. Through close monitoring early detection of impairment of the glucose and lipid metabolism and occurrence of CVE is supported.

7.6 Tolerability/acceptability

Not applicable

7.7 Resource utilization

Not applicable

7.8 Health-related Quality of Life (HRQOL)

In CML, the introduction of TKI treatment led to a decisive extension of survival time. As a consequence, issues such as reducing side effects, symptom relief and patients' satisfaction have moved into focus in order to assess the adequacy of medical strategies.

Patients will be asked to complete the EORTC QLQ-CML 24, an internationally developed disease specific HRQOL questionnaire for CML patients, together with the EORTC-QLQ C30 questionnaire. The QLQ-CML 24 has been developed according to the EORTC guidelines involving a large sample of patients (655 CML patients in 10 countries). The questionnaire is composed of four mulit-item scales and two single-item scales. The module consists of 24 items assessing symptom burden, impact on daily life and on worry/mood, body image problems, and satisfaction with care and social life. The items are measured on four levels: not at all, a little, quite a bit and very much. The EORTC QLQ-CML 24 is a supplement to the EORTC-QLQ C30 and intended to be used in conjunction (Efficace et al., 2014, Aaronson et al., 1993).

QoL will be evaluated at Screening/Baseline (within 7 days prior to study inclusion), and at 3, 6, 12, 18, 24 months.

The patient informed consent form explains the patients that they will have a regular QoL assessment while involved in the trial. The questionnaires will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. Patients will be asked to fill out the questionnaires as completely and accurately as possible. Patient's refusal to complete all or any part of a questionnaire should be documented in the study data capture system and should not be captured as a protocol deviation.

The site personnel should check the questionnaire for completeness and ask the patient to complete any missing responses. The original questionnaire will be kept with the patient's file as the source document.

Completed questionnaire(s) and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs.

7.9 Pharmacokinetics

n.a.

7.10 Pharmacogenetics/pharmacogenomics

n.a.

7.11 Other biomarkers

n.a.

8 Safety monitoring

8.1 Adverse events

8.1.1 Adverse event definition and reporting

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g. hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible,

rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 to 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 AEs should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. In addition to direct questioning of the patient, the Investigator should review the patient diary and discuss potential AEs with the patient during each visit. Adverse events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each AE should be evaluated to determine:

• The severity grade (CTCAE Grade 1-4);

• Its duration (Start and end dates);

• Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes);

• Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable);

• Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy);

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

• Whether it is serious, where a SAE is defined as in 8.2.1

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

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Natural progression or deterioration of the malignancy under treatment (including progression to accelerated phase or blastic phase and death due to disease progression) will be recorded as part of the efficacy evaluation and should not be reported as an AE/SAE.

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 of special interest

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

• Ischemic Heart Disease (IHD): angina pectoris, coronary artery disease, acute myocardial infarction and coronary artery stenosis

• Ischemic Cerebrovascular Events (ICVE): ischemic cerebrovascular accident, and transient ischemic attack

• Peripheral Artery Occlusive Disease (PAOD): intermittent claudication, arterial stenosis of a limb

If patients experience ischemic vascular or ischemic cardiovascular events, carefully consider protocol guidance for dose reduction or study drug discontinuation (Protocol Table 6.1).

The Investigator should ensure that the patient is assessed by a vascular or cardiovascular specialist. It is recommended that the standard of care for concurrent ischemic vascular or cardiovascular events should be given to the patients while they are receiving nilotinib therapy. All patients should have their risk factors for such diseases appropriately managed and follow the current recommendations (please see also section 6.6.8).

The Study Steering Committee will be informed on regular basis on the Grade 2/3/4 ischemic vascular or cardiovascular events occurring to the patients enrolled in the trial.

8.1.2 Laboratory test abnormalities

Laboratory abnormalities that constitute an Adverse Event in their own right (are considered clinically significant, induce clinical signs or symptoms, require dose reduction or temporary or permanent study drug discontinuation or require concomitant therapy), should be recorded on the Adverse Event CRF page. Whenever possible, a diagnosis, rather than a symptom should be provided. Laboratory abnormalities that meet the criteria for an Adverse Event 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 or laboratory abnormality (severe) as per CTCAE (if applicable) does not automatically indicate an 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 and is still, by definition, an AE.

8.2 Serious adverse events

8.2.1 Serious adverse event definition, treatment and follow-up

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - 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 the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- 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

8.2.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is 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. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the German Novartis Clinical Safety & Epidemiology Department. Causality for each reported serious event on the SAE report form must be assessed as either as "Suspected" or "Not Suspected" to the study drug. No other term such as "Probable", "Plausible", "May be" or "Could be" etc. should be used for causality assessment. The telephone and telefax number of the contact persons in the German department of Clinical Safety and Epidemiology, 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 person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Clinical Safety & Epidemiology 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 Pregnancy reporting

To ensure patient safety, each pregnancy in a patient on study drug 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.

Instances of pregnancies and positive pregnancy tests should be collected for all patients who have conceived after receiving study medication. Pregnancies that are noted prior to administration of study medication but after signing informed consent may require reporting if they are considered to be associated to the conduct of the study by the investigator.

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

8.4 Reporting of adverse events and pregnancies after the last dose of study drug taken

All AEs, SAEs, and pregnancies which occurred within 30 days after intake of last dose of study drug should be reported.

8.5 Steering Committee

The Steering Committee (SC) will be established comprising external experts in the field of CML, one cardiologist/angiologist and Novartis representatives from the Clinical Trial Team. The SC will be supported and advised by a patient advocate.

The SC will suggest modifications to the trial protocol, ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require and consider patient cases where further discussion is required. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules.

9 Data review and database management

9.1 Site monitoring

Before study initiation, at a site initiation visit, a Novartis representative will review the protocol and eCRF 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 eCRF, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that drug is being accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data collection

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the Remote Data Capture (RDC) system until they have been trained. Designated investigator staff will enter the data required by the protocol into the Novartis

eCRFs using the Investigator's own computer. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

9.3 Database management and quality control

Novartis staff (or designated CRO) review the eCRFs entered by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and make any necessary changes to the data.

Concomitant 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.

Laboratory samples for molecular monitoring will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO) and the investigational site.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made by joint written agreement between the Trial Statistician and Statistical Reporting and the Clinical Trial Leader.

10 Data analysis

The data will be analyzed by Novartis and/or by the designated CRO. Any data analysis carried out independently by the investigator(s) should be submitted to Novartis before publication or presentation.

It is planned that the data from all centers that participate in this protocol will be used, so that an adequate number of patients will be available for analysis.

Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements and safety observations and measurements.

10.1 Populations for analysis

The Full Analysis Set (FAS) will consist of all patients that entered study and received at least one dose of study drug and have at least one post-baseline assessment of the primary efficacy variable.

The Safety Set will consist of all patients that received at least one dose of study drug and had at least one post-baseline safety assessment. Of note, the statement that a patient had no adverse events also constitutes a safety assessment.

The Per-Protocol Set will consist of all patients who did not show major deviations from the protocol procedures that might have an impact on the study outcome. Criteria that are assumed to have such an impact will be defined in the data validation document (VAP).

The key efficacy analysis will be performed for both, the FAS and the PPS set. The FAS is regarded as primary.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be summarized descriptively for both the Safety Set and the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

10.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

All study medication data will be summarized using the safety set.

Time on treatment, duration of exposure, percentage of days on treatment, average dose intensity, actual daily dose and relative dose intensity will be summarized for these above safety subsets.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized.

10.4 Analysis of the primary objective(s)

The primary objective of the study is to evaluate the proportion of patients that achieve deep molecular response $MR^{4.5}$ (IS) at 24 months of study treatment, measured in a standardized EUTOS $MR^{4.5}$ laboratory

10.4.1 Variable

The primary efficacy variable is the rate of $MR^{4.5}$ at 24 months of study treatment measured in a standardized EUTOS $MR^{4.5}$ laboratory. $MR^{4.5}$ is defined as either (i) detectable disease $\leq$ 0.0032% $BCR\text{-}ABL^{IS}$ or (ii) undetectable disease in cDNA with 32 000 – 99 999 ABL1 transcripts or 77 000 – 239 999 GUSB transcripts.

Molecular response (MMR, MR^4 and $MR^{4.5}$) will be calculated for patients with b2a2 and/or b3a2 BCR-ABL transcripts only. Patients with alternative transcripts will be excluded for the analysis, because their transcripts cannot be used for deep MR or MMR determination.

10.4.2 Statistical hypothesis, model, and method of analysis

The rate of $MR^{4.5}$ (IS) at 24 months of study treatment will be computed by dividing the number of patients who fit the definition of response at 24 months by the total number of patients in the analysis set. The corresponding 95% confidence interval will be computed as well.

10.4.3 Handling of missing values/censoring/discontinuations

Only patients with a $MR^{4.5}$ at 24 months of study treatment, or if the assessment at this time point is missing, with a $MR^{4.5}$ at 21 months are considered responders. Patients dropping out early or not providing sufficient data for any other reason will be considered as early discontinuation or not evaluable, respectively, and will be included in the analysis set as non-responders, even if a $MR^{4.5}$ was previously achieved. Any patient who achieves $MR^{4.5}$ before 24 months, but is no longer in $MR^{4.5}$ at 24 months or progressed (or is no longer in $MR^{4.5}$ at 21 months if evaluation at 24 months is missing), will be considered as a non-responder.

10.4.4 Supportive analyses

The primary analysis will also be repeated on per-protocol population as a sensitivity analysis of robustness of the results. Additionally, primary analysis will be stratified for gender.

10.5 Analysis of secondary objectives

For all computations on molecular endpoints, patients with atypical transcripts will not be considered, i.e. will be excluded from the analysis, because they cytogenetically respond as normal patients, but their transcripts cannot be used for molecular response determination.

10.5.1 Efficacy (secondary)

10.5.1.1 Secondary efficacy variables

MR^4 (IS)

- MR^4 (IS) is defined in this study as either (i) detectable disease ≤0.01% $BCR\text{-}ABL^{IS}$ or (ii) undetectable disease in cDNA with 10 000 – 31 999 ABL1 transcripts or 24 000 – 76 999 GUSB transcripts.
- The rate of MR^4 (IS) at 24 months of study treatment will be computed by dividing the number of patients who fit the definition of response at 24 months by the total number of patients in the analysis set.

MMR

- MMR is defined as a ≥3 log reduction from the standardized baseline or ≤ 0.1% BCR-ABL^{IS}
- The rate of MMR at 12 months of study treatment will be computed by dividing the number of patients who fit the definition of response at 12 months by the total number of patients in the analysis set

CCyR

- Complete cytogenetic response is defined as 0% Ph+ metaphases
- Rate of CCyR at 6 months of study treatment will be calculated by dividing the number of patients who fit the definition of response at 6 month by the total number of Ph+ patients in the analysis set

Outcome

- Time to progression to AP/BC is defined as the time from the date of start of study treatment to the date of earliest transformation to AP/BC, or CML-related death. Rates of progression at various time points will also be provided.
- Progression-free survival is defined as the time from the date of start of study treatment to the date of event defined as the first documented disease progression to AP/BC or the date of death from any cause, whichever is earlier.

10.5.1.2 Methods of analyses

The rate of molecular responses at certain time points will be presented together with an exact 95% confidence interval.

Kaplan Meier's product limit estimates will be used for time to event endpoints, such as time to progression to AP/BC and progression-free survival (PFS). The estimated rates by Kaplan Meier's method at various time points will also be provided.

For time to progression to AP/BC and PFS patients will be censored if one of the following situations occurs:

- If a patient does not experience an event before the cut-off date for the analysis, censoring time will be the last assessment date before the cut-off date
- If a patient discontinues study treatment prior to experiencing an event, then the patient will be censored at the date of last assessment prior to the date of discontinuation.

10.5.1.3 Handling of missing values

For MMR and CCyR assessment at a specific time point, only patients with response which occurs or is sustained at the specific time point are considered responders; e.g. a patient who achieves MMR before 12 months but is no longer in MMR at 12 months (or progressed), will be considered as a non-responder at 12 months. The same applies for all time points and response variables. Patients dropping out early or not providing sufficient data for any other

reason will be considered as early discontinuation or not evaluable, respectively, and will be included in the analysis set as non-responders.

10.5.2 Safety

All the safety analyses will be based on the Safety Population.

Adverse Events

The incidence of treatment-emergent AEs (new or worsening from screening visit) will be summarized by MedDRA System Organ Class and Preferred Term, severity (based on CTCAE grades), type of AE, and relation to study treatment.

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE.

Laboratory abnormalities

For laboratory tests covered by the CTCAE version 4.03, the study's biostatistican will grade laboratory data accordingly. Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology and clinical chemistry:

- Number and percentage of patients with laboratory abnormalities, by parameter and worst post-baseline CTCAE grade. Each patient will be counted only for the worst grade observed post-baseline, regardless of the baseline status;
- Shift tables using CTCAE grades to compare baseline to the worst on treatment value;
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, [redacted] might be specified in the RAP.

Other safety data

Other safety data collected (e.g. ECG, vital signs etc.) will be listed and summarized using descriptive statistics as appropriate. Notable values may be flagged. Notable/abnormal values for safety data will be further specified in the RAP.

10.5.3 Tolerability

n.a.

10.5.4 Resource utilization

n.a.

10.5.5 Health-related Quality of Life

Descriptive statistics will be provided for the EORTC QLQ-C30 in combination with the EORTC QLQ-CML 24 questionnaire (including absolute change from baseline) up to the end of study for the FAS. Additional analysis may be performed and details will be prescribed in the analysis plan.

10.5.6 Pharmacokinetics

n.a.

10.5.7 Pharmacogenetics/pharmacogenomics

n.a.

10.5.8 Biomarkers

n.a.

10.5.9 PK/PD

n.a.

[redacted]

10.7 Interim analysis

An interim analysis of baseline and follow-up data is planned after the first 38 patients included in the study reach the end of month 6 visit, as of April 2017 in order to evaluate the integrity of the collected data. No evaluation of the primary endpoint will be conducted and therefore no adjustments with regard to the alpha level will be made. The rational for interim analysis is to check the integrity of the data.

The interim analysis will be purely descriptive in nature and include patient characteristics, vital signs, Sokal risk score, EUTOS score, ESC risk score, ECOG performance status, hematologic and blood chemistry laboratory values, RQ-PCR results, medical history and adverse events. These parameters are described in panels DM, ZC, VS, SRS, QSEUT, QSESC, QSECOG, LBLGH, B2, B1, MH, FACM, SU, EG, LBLGC, AE and LBLGU. For panel VS, QSESC, LBLGH, B2, B1, FACM, SU, EG, LBLGC, AE and LBLGU analysis will be performed for initial visit and all sub sequential visits till end of month 6.

10.8 Sample size calculation

The aim of the current study is to confirm the $MR^{4.5}$ rates of nilotinib in a broad population using the EUTOS $MR^{4.5}$ ('European Treatment and Outcome Study for CML') standardized molecular laboratories.

Therefore sample size is based on the precision of estimate computation; i.e. the 95% confidence interval of the proportion of patients with $MR^{4.5}$ at month 24.

Assuming a $MR^{4.5}$ rate at 24 months to be 25%, a total of 171 patients will allow for a precision of +/- 6,5 %.

10.9 Power for analysis of critical secondary variables

n.a.

11 Discussion and rationale for study design features

Objectives and treatment design:

Primary objective of this Phase-IV study is to determine the rate of $MR^{4.5}$ in newly diagnosed CML patients after 2 years of nilotinib treatment and is investigated in an open-label single arm design. The defined secondary objectives can be assessed through a single arm design accordingly.

Population criteria:

This study is open to all newly diagnosed patients with CML in chronic phase which the investigator intends to treat with nilotinib 300mg BID in accordance with treatment guidelines (e.g. ELN-Guidelines, (Baccarani et al., 2013)) and the label of the drug. For reasons of the study conduct and patient safety these patients will furthermore have to comply with the stated in- and exclusion criteria in Section 5.

Study drug dose:

Nilotinib 300mg BID is the approved dose for newly diagnosed CML patients in chronic phase and is recommended as one of three possible TKIs for the first-line treatment of CML-CP by ELN guidelines (Baccarani et al., 2013).

Assessments:

BCR-ABL expression in peripheral blood will be assessed by RQ-PCR, performed in EUTOS laboratories. The EUTOS laboratories are certified for performing this assessment reproducibly with the most accuracy to identify $MR^{4.5}$. The relevance for assessing deep molecular response $MR^{4.5}$ is provided in Section 2.

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Appendix 1: Ethical considerations and administrative procedures

Regulatory and ethical compliance

This clinical study was designed and 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, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Responsibilities of the investigator and IRB/IEC/

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board / Independent Ethics Committee (IRB/IEC) before study start. Approval letters concerning protocol and informed consent will be filed by Novartis. 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, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

Informed consent procedures

Eligible patients may only be included in the study after providing written, IRB/IEC-approved informed consent.

Women of child bearing potential should be informed that taking the study drug 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.

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.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study.

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 trial 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 it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

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. Only amendments that are required for patient safety may be implemented prior to IRB/IEC 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 within 10 working days.

Discontinuation of the study

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

Publication of study design 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.

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.

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.

Audits and inspections

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

Appendix 2: List of CYP3A4 inducers, inhibitors and substrates

Medications that can induce CYP3A4

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

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

Note:

Inducer classification:

- Strong inducers may result in a substrate area under curve (AUC) decreased by ≥ 80%.
- Moderate inducers may result in a substrate AUC decreased by 50-80%.
- Weak inducers may result in a substrate AUC decreased by 20-50%.

This list is compiled based on the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ **for updates or more details, as well as the complete list of Cytochrome P450 substrates.**

Medications that can inhibit CYP3A4

Strong inhibitors	Moderate inhibitors	Weak inhibitors
clarithromycin	amprenavir	alprazolam
conivaptan	aprepitant	AMD070
Indinavir	atazanavir	amlodipine
itraconazole	cimetidine	azithromycin
ketoconazole	ciprofloxacin	bicalutamide
lopinavir	darunavir	cranberry juice
mibefradil	diltiazem	chlorzoxazone
nefazodone	elvitegravir	cilostazol
nelfinavir	erythromycin	cyclosporine
posaconazole	fluconazole	fluvoxamine
ritonavir	grapefruit juice	ginkgo
saquinavir	imatinib	goldenseal
telithromycin	schisandra sphenanthera	isoniazid
troleandomycin	tipranavir	lacidipine
voriconazole	tofisopam	M100240
	verapamil	nilotinib
		oral contraceptives (e.g. drospirenone, norgestimate, and ethinyl estradiol)
		peppermint oil
		propiverine
		ranitidine
		ranolazine
		roxithromycin
		Seville orange juice
		sitaxentan
		tabimorelin

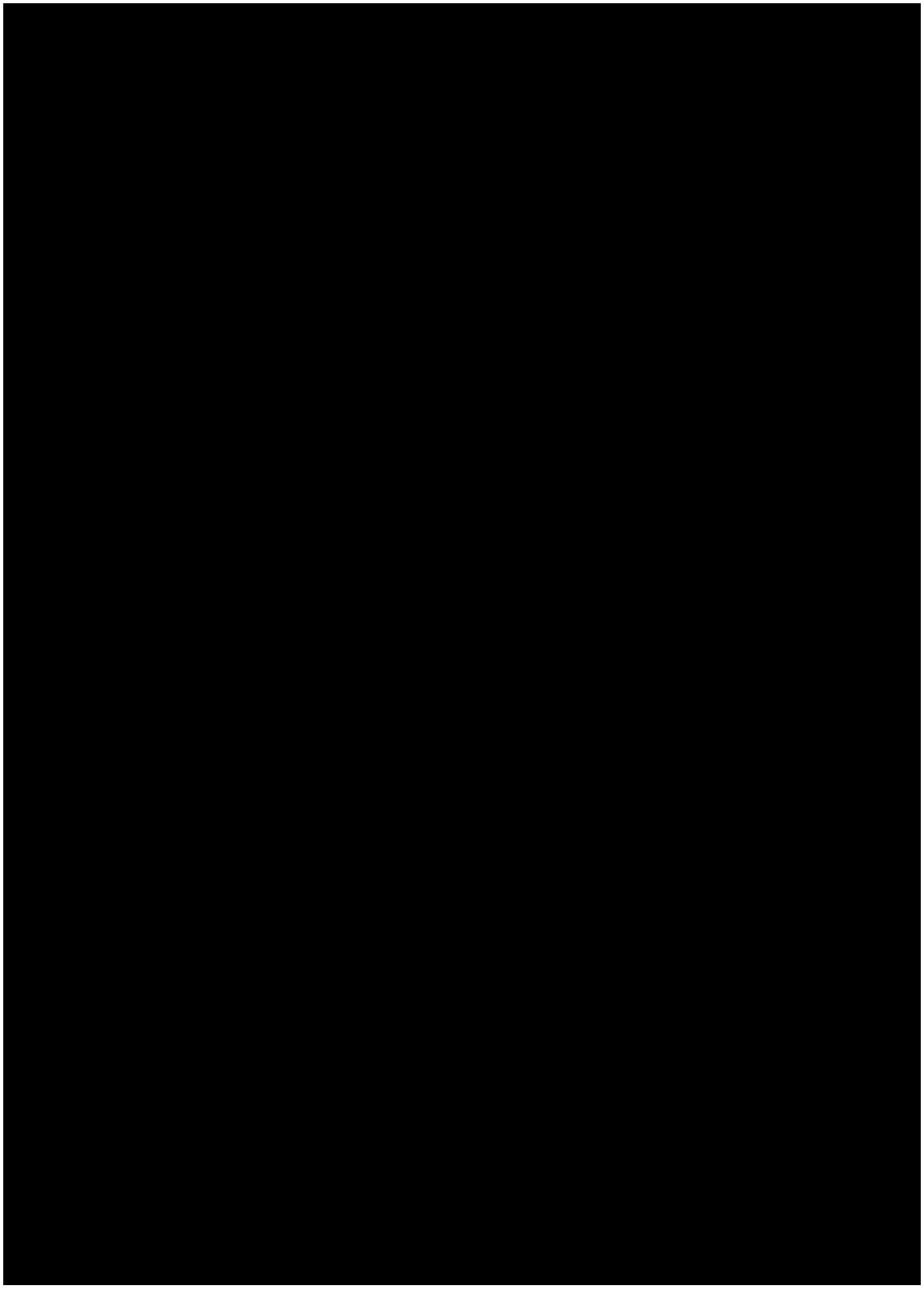
Note:

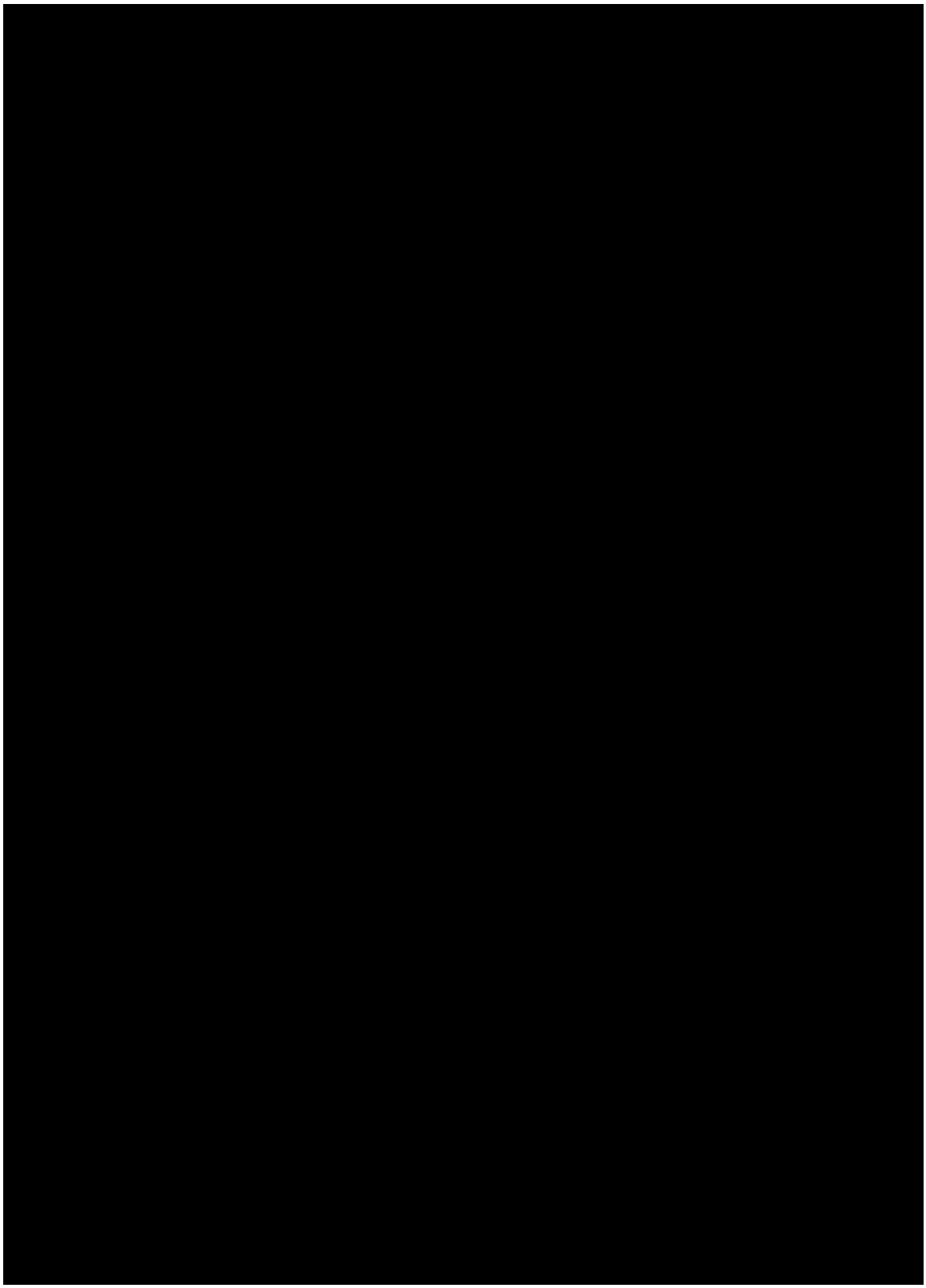
Inhibitor classification:

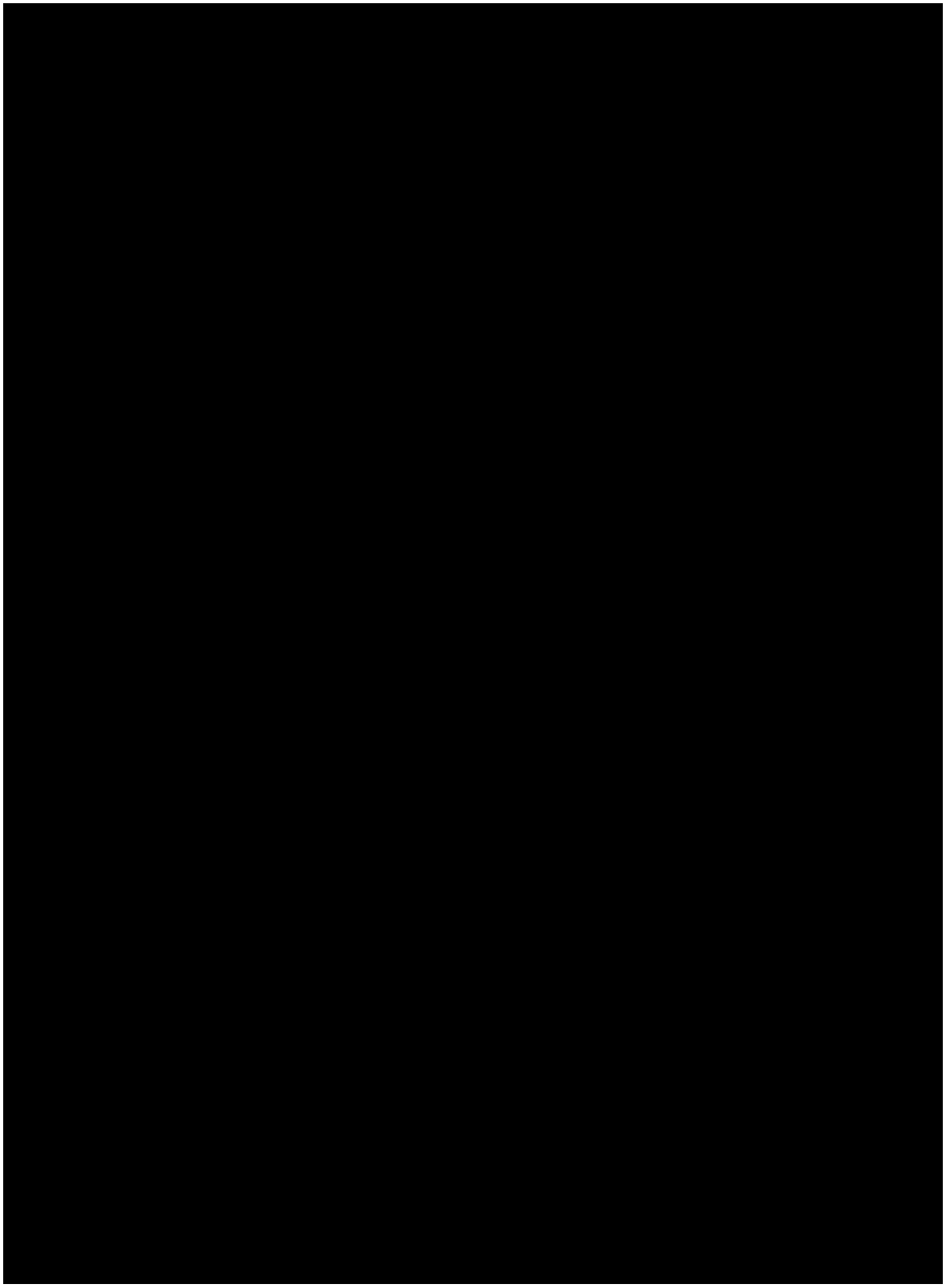
- Strong inhibitors may result in a substrate AUC > 5-fold increase.
- Moderate inhibitors may result in a substrate AUC ≥ 2-fold increase and < 5-fold increase.
- Weak inhibitors may result in a substrate AUC ≥ 1.25-fold increase and < 2-fold increase.

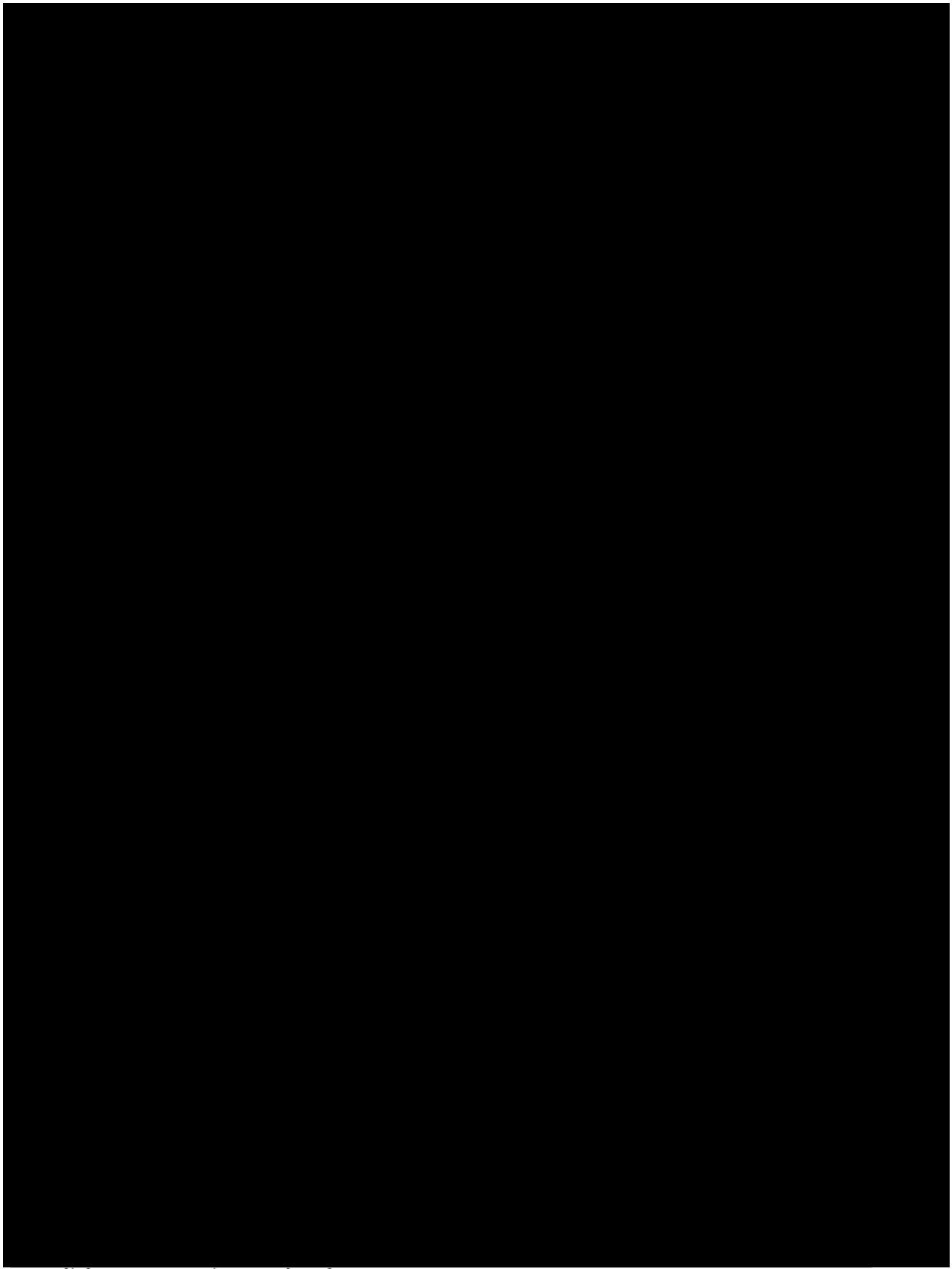
This list may not be comprehensive and may be updated periodically. Refer to **http://medicine.iupui.edu/clinpharm/ddis/main-table/ for updates or more details, as well as the complete list of Cytochrome P450 substrates.**

13 Appendix 3: Quality of Life Questionnaires









14 Appendix 4: ESC Risk SCORE chart