Redacted protocol

Observational Study Protocol

CAMN107AAT01

A PROSPECTIVE NON-INTERVENTIONAL SAFETY STUDY IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA RECEIVING NILOTINIB IN DAILY PRACTICE ACCORDING TO UPDATED GUIDELINES

Sponsor:

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PASS information

EU PAS register number	Study not yet registered
Active substance	Nilotinib (CAMN107, Tasigna®)
Research question and objectives	[redacted]
Countries of study	Austria, Germany
Marketing authorization holder	Novartis Pharma GmbH
MAH contact person	[redacted]

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1 Responsibilities

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Projectmanager eCRF/Datamanagement

[redacted]

2 List of Abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
AP	Accelerated Phase
ALAT	Alanine aminotransferase / GPT
AMG	Medicinal Products Act *[Arzneimittelgesetz]*
ASAT	Aspartate aminotransferase / GOT
BC	Blast Crisis

BCR-ABL	Breakpoint Cluster Region – Abelson
CCyR	Complete cytogenetic response
CFR	Code of Federal Regulations
CHR	complete hematologic response
CML	Chronic myeloid leukemia
CP	Chronic phase
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
DMP	Data management plan
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FISH	Fluorescence *in situ* hybridization
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Major molecular remission
NIS	Non-interventional study
PAOD	Peripheral Arterial Occlusive Disease
PASS	Post-authorization Safety Study
Ph+	Philadelphia chromosome-positive
PT	Preferred term (MedDRA)
RMP	Risk Management Plan
PSUR	Periodic Safety Update Report
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SDV	Source data verification
SOC	System organ class (MedDRA)
SOP	Standard operating procedure
SPC	Summary of product characteristics

3 Synopsis

Background and rationale:

Nilotinib (Tasigna®, AMN107) is a rationally designed second generation BCR-ABL tyrosine kinase inhibitor with improved target specificity over imatinib. Its efficacy and safety in the treatment of patients who are resistant to or intolerant of imatinib (Kantarjian 2006, Kantarjian 2007, le Coutre 2008) led to the approval in second line treatment of CML-CP and AP and to further evaluation of its use in the treatment of newly diagnosed CML in CP. Data from three independent study groups have demonstrated high rates of complete cytogenetic and major molecular responses (Cortes 2009, O'Dwyer 2009, Rosti 2009a, Rosti 2009b) in patients with newly diagnosed CML. [redacted]

This is a Post Authorization Safety Study according to the EU Volume 9a of the Rules Governing Medicinal Products in the European Union

Study objectives:

[redacted]

Number of participating centers and selection of patients

This non-interventional multi-center study will be conducted in up to 10-15 hematology-oncology institutions in Austria and Germany in a regional distribution pattern and will include 100 male or female patients with

- newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (CML) in chronic phase
- Philadelphia chromosome positive CML in chronic phase with resistance to or intolerance of prior therapy including imatinib (assessed according to current ELN recommendations).

All patients will be treated with nilotinib in line with established clinical practice and under special consideration of current treatment guidelines and local recommendations (Baccarani *et al.*, 2009, Valent *et al.*, 2011, Kim *et al.* , 2012).

Patients observed in this NIS are not allowed to participate in any other simultaneously conducted clinical study as this does not represent routine clinical practice.

Observation period:

The observation period per patient will be 4 years. Observation follow-up intervals are not

predetermined but should be based on routine clinical practice as well as the individual situation of each patient. Since this is an observational study in the context of routine clinical practice, no actual visit schedule will be dictated by the observational plan. Patient visits should be performed as per investigator discretion under special consideration of local guidelines and published recommendations (Baccarani *et al.*, 2009, Valent *et al.*, 2011, Rosti *et al.*, 2011, Kim *et al*., 2012).

This study is non-interventional or observational in nature and does not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. Available data from routine clinical management of the patients will be collected at patients' visits to their site (e.g. at baseline and after 3, 6, 9, 12, 18, 24, 36 and 48 Month) if available.

Patient population:

Patients eligible for participation to this non-interventional study must fulfill all of the following criteria:

- Patients will be treated with nilotinib. Nilotinib therapy should not be prescribed for the purpose of inclusion in this NIS, but solely for clinical therapeutic indication. Nilotinib treatment will start after the baseline documentation.
- Patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (CML) in chronic phase

  OR

  Patients with Philadelphia chromosome positive CML in chronic phase with resistance to or intolerance of prior therapy including imatinib
- patients are eligible for and have no contraindication against nilotinib according to the SPC and according to updated local treatment recommendations (e.g. Valent *et al.*, 2011, Kim *et al.* , 2012) if applicable;
- patients received [comprehensive] information about this NIS and signed the

Informed Consent Form (ICF);

For all patients, a written informed consent to documentation should be obtained. The enclosed SPC should be consulted with respect to the indication of nilotinib therapy as well as regarding contraindications and possible side effects.

Analyzed parameters:

- Assessment of **Safety and tolerability** by Documentation of clinical status and reporting of tolerability and all AEs (serious and non-serious) during treatment.

Overall documentation may include:

- Complete case history, including [redacted]
- [redacted].
- The number of patients [redacted]
- Documentation of [redacted]

Statistical methods

There are no predefined hypotheses regarding the incidence of specific safety outcomes, the magnitude of effectiveness or treatment practices. Descriptive statistical methods will be used for all variables of evaluation.

Ethical requirements and regulations

Prior to the start of the study, the NIS will be submitted for review by an Ethics Committee. Prior to the initiation of its conduct, the NIS will be forwarded for review/notification to a relevant authority (in Austria to the Medicines Market Surveillance *[Medizinmarktaufsicht* /

Bundesamt für Sicherheit im Gesundheitswesen]), in Germany to the BfArM.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Patients must be informed accordingly, and will be asked to provide their informed consent on data-handling procedures in accordance with national regulations in place in each participating country.

Timeline

The study will be conducted between the first quarter of 2013 and the first quarter of 2020.

4 Introduction and rationale

4.1 Overview of chronic myeloid leukemia and response criteria

Chronic myeloid leukemia (CML) accounts for approximately 5-10% of myeloid leukemia in adults, and it belongs to the group of chronic myeloproliferative diseases (Faderl et al., 1999; Sawyers, 1999). CML is a clonal myeloproliferative disease of hematopoietic stem cells, leading to an increase in the number of granulocytic and other myeloid (precursor) cells. CML is characterized by a specific chromosomal translocation, the Philadelphia (Ph) chromosome, resulting from exchange of genetic material between chromosomes 9 and 22 (t(9;22)(q34;q11)) (Nowell et al., 1960; Rowley, 1973). The related molecular defect is the fusion of *ABL1* with the *BCR* gene which yields the BCR-ABL1 oncoprotein (Faderl et al., 1999). BCR-ABL1 confers a growth advantage to leukemic cells, increases their proliferation and cytokine-independent growth, inhibits apoptosis and alters adhesion properties of neoplastic cells (Sawyers, 1999; Deininger et al., 2000; Van Etten, 2004). In most patients, the diagnosis is confirmed cytogenetically by demonstrating the presence of the Ph chromosome, and by molecular testing for BCR-ABL1.

The clinical course of CML includes three phases. The relatively stable chronic phase is characterized by an increased number of white blood cells (WBC) and/or platelets, absence of marked basophilia, and less than 10% blasts in blood and bone marrow. Accelerated phase (AP) is defined by 15%-29% blast cells in blood or bone marrow or blast cells plus promyelocytes in blood or bone marrow more than 30%, with blast cells less than 30%, >20% basophils in blood or bone marrow, thrombocytopenia (<100,000/µL) or thrombocytosis (>1,000,000/µL), cytogenetic evidence of clonal evolution in addition to the Ph chromosome and increasing splenomegaly or WBC, unresponsive to therapy (Baccarani et al. 2006). The terminal phase, called blast crisis (BC), is characterized by ≥20% blasts in blood or bone marrow, extramedullary blast proliferation and clusters of blasts in bone marrow biopsy (Vardiman *et al.*, 2002). Once the blast crisis stage is reached, the median survival is only a few months (average duration of 3-6 months according to Enright and McGlave, 2000).

During recent decades therapy of CML contained cytotoxic agents (such as hydroxyurea and busulfan) and interferon-α as well as allogeneic stem cell transplantation. The latter is still recognized as the only curative therapy, albeit it is not always feasible or effective, and it carries an appreciable risk for side effects and complications (Faderl, et al. 1999). Response to CML therapy is measured by assessing different parameters whereas three categories of response have been defined:

- hematologic response, i.e. normalization of hematopoiesis. A complete hematologic response (CHR) is characterized by platelets < 450 000/µL, and WBC count < 10 000/µL, and differential blood count without immature granulocytes and < 5% basophils, and non-palpable spleen
- cytogenetic response: i.e. reduction of Ph+ metaphases in bone marrow (CCyR is 0% Ph+ cells)
- molecular response: i.e. reduction in the BCR-ABL/ABL transcript ratio (major molecular response, MMR, is ≤ 0.1%) in peripheral blood or bone marrow).

4.2 Overview of nilotinib (Tasigna®)

Nilotinib (Tasigna®, AMN107) is a second-generation BCR-ABL tyrosine kinase inhibitor. It is a more potent BCR-ABL inhibitor than imatinib, and it inhibits the catalytic activity of the BCR-ABL molecule in various cell lines with an IC_{50} value of 22-42 nM (imatinib, IC_{50} 196-495 nM). Additionally, nilotinib has an anti-proliferative effect on cell lines, expressing BCR-ABL (nilotinib, IC_{50} 4-34 nM; imatinib, IC_{50} 61-577 nM). Another clinically relevant feature of nilotinib in physiologically relevant concentrations is the inhibition of protein tyrosine kinase activity of certain imatinib-resistant BCR-ABL forms with point mutations in the kinase domain (including E255V, F317L, M351T and F486S) (Weisberg, *et al.* 2005).

In clinical studies, nilotinib demonstrated excellent efficacy and good tolerability in CML patients with imatinib-resistance or -intolerability (Kantarjian *et al.* 2006, Kantarjian *et al.* 2007, Le Coutre *et al.* 2008); hence, it obtained approval in November 2007 as a second-line agent in the treatment of CML. In December 2010, therapy regimen with twice-daily (bid) 300 mg nilotinib received approval as a first-line therapeutic modality in adult patients with newly-

diagnosed Philadelphia chromosome-positive myeloid leukemia (Ph+ CML) in the chronic phase (CP). The approval is based on results of the ENESTnd study (CAMN107A2303) which established superiority of nilotinib over imatinib 400 mg q.d. with respect to cytogenetic and molecular response rates (Saglio *et al*., 2010; Kantarjian *et al.*, 2011). Most noteworthy, the progression rate (transition to advanced CML phases—AP and BC) proved to be significantly lower for both nilotinib arms (<1% for both dosage regimens) than for imatinib patients (4%).

4.3 Rationale of the study

Currently available data confirming the safety of nilotinib in CML treatment is based on controlled clinical studies with a predefined patient population. [redacted].

Nilotinib is generally well tolerated, with manageable side effects. Besides hematologic side effects, nilotinib-treated patients may develop increases in pancreatic enzymes, bilirubin, and fasting glucose level (Kantarjian *et al.* 2011). Other non-hematologic adverse events include diarrhea, folliculitis-like skin rash, and bleeding. There are a few reports of severe peripheral arterial occlusive disease (PAOD) and other vascular occlusive events (infarction) in patients receiving nilotinib (Aichberger *et al.*, 2011; Le Coutre *et al.*, 2011; Tefferi and Letendre, 2011, Quintás-Cardama *et al.*, 2012). In the ENESTnd study, 6 cases of PAOD have been reported to date in both nilotinib arms, while no cases have been reported in the control imatinib arm (Kantarjian *et al.*, 2011). In light of these reports, Novartis undertook a review and assessment of PAOD cases, and results were discussed with an external advisory board. In conclusion, a causal relationship between the events and nilotinib could neither be confirmed nor ruled out; hence, a recommendation to exclude patients with a risk of PAOD secondary to therapy with

nilotinib was not made. As a consequence the SPC was updated with PAOD being classified as uncommon adverse reaction (≥1/1,000 to <1/100) based on its reported frequency. Moreover, treatment guidelines have been updated to ensure appropriate patient treatment and monitoring (Valent *et al.*, 2011, Kim *et al.* , 2012). This study aims to evaluate the safety of nilotinib as per SPC and the implementation of current guidelines in daily clinical routine (Baccarani *et al.*, 2009, Valent *et al.*, 2011, Rosti *et al.*, 2011, Kim *et al*., 2012).

4.4 Study objectives

[redacted]

This study is non-interventional or observational in nature and does not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. Available data from routine clinical management of the patients will be collected at patients' visits to their site (e.g. at baseline and after 3, 6, 9, 12, 18, 24, 36 and 48 Month) if available.

5 Design of the study

This is a Post Authorization Safety Study according to the EU Volume 9a of the Rules

Governing Medicinal Products in the European Union for patients diagnosed with CML in the chronic phase. The study is planned to document patients diagnosed with CML in the chronic phase exposed to nilotinib with the objective of enrolling at least 100 patients exposed to nilotinib within 3 years. A minimum follow-up of at least 4 years will be allowed for all patients enrolled. Nilotinib must not be prescribed for the purpose of participation to the study. First treatment with nilotinib will start after the baseline documentation.

The study will be conducted in compliance with all applicable national and local regulations.

5.1 Study centers and patients

This is a multi-center NIS, conducted in approximately 10-15 hematology-oncology practices/centers, hence ensuring a representative sample of the population for the involved study centers.

The sponsor and its authorized personnel will inform the participating physicians about the goals and modalities of this non-interventional study. Therapy with nilotinib should be documented over a 4-year observation period.

This non-interventional study will include approximately 100 male or female patients with newly-diagnosed Ph+ CML in CP, or Ph+ CML CP patients with an inadequate response or toxicities to prior therapy including imatinib (assessed according to current ELN recommendations). We will enroll in this observational study patients being under treatment with nilotinib administered in line with the SPC and in accordance with the routine clinical practice, also considering recommendations of updated guidelines ELN (Baccarani *et al.*, 2009, Valent *et al.*, 2011, Kim *et al.*, 2012) if applicable. Observation follow-up intervals are not predetermined for each patient; instead, they should be based on routine clinical practice.

The following types of patients are suitable for enrollment into this NIS:

- Patients who will be treated with nilotinib and:
  - newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (CML) in the chronic phase

    OR

  - Patients with Philadelphia chromosome positive CML in the chronic phase with resistance to or intolerance of prior therapy including imatinib
- Patients are eligible for and have no contraindication against nilotinib according to the SPC and according to updated local treatment recommendations (e.g. Valent *et al.*, 2011, Kim *et al.*, 2012) if applicable;
- Patients received [comprehensive] information about this NIS and signed the Informed Consent Form (ICF);
- Patients are not allowed to simultaneously participate in any other clinical study because this does not represent routine clinical practice and it hence defeats the purpose of a NIS.

For all enrolled patients, a written informed consent to documentation should be obtained. The enclosed SPC should be consulted with respect to the indication of nilotinib therapy as well as regarding contraindications and possible side effects. Nilotinib therapy should not be prescribed for the purpose of inclusion in this NIS, but solely for clinical therapeutic indication.

5.2 Observation period

In order to achieve conclusive results, relevant to the set goals, the observation period of therapy with nilotinib should not exceed 48 months. PASS timeline:

Start of patient observation period	[redacted]
End of patient enrollment	[redacted]

End of observation period	[redacted]
Deadline for submission of documentation forms	[redacted]
Final Report due	[redacted]

Only data entered into the eCRF within 2 months of the conclusion of the observation phase may be used for statistical evaluation and remuneration purposes (electronic signature required).

5.3 Observation parameters

During this non-interventional study, solely the diagnostic measures and clinically indicated examinations conducted in line with the routine clinical practice will be documented.

5.3.1 Start of observation / baseline examination

- Demographic data (including year of birth and gender);
- Documentation of patient-reported medical history [redacted]);
- Documentation of diagnostic assessments [redacted] in line with the updated guidelines (Valent *et al.*, 2011, Kim *et al.*, 2012), if documented;

- Features of disease (including date of diagnosis and its main characteristics, ECOG Performance Status – if conducted) as well as possible pretreatment with hydroxyurea or imatinib;
- Date of the first cytogenetic, hematologic and molecular examination;
- Co-morbidities and concomitant therapies.

5.3.2 Follow-up examinations during the observation period

Taking into consideration the precautions and recommendations specified in the SPC, a complete blood count and serum chemistry [redacted] should be performed at regular intervals.

Follow-up examinations will be performed according to routine clinical practice and recently published guidelines and recommendations (Baccarani *et al.*, 2009; Valent *et al.*, 2011, Kim *et al*., 2012), and documented for the purposes of this non-interventional study approximately at months 3, 6, 9, 12, 18, 24, 36 and 48 after the start of nilotinib therapy.

Additional medical examinations used in clinical routine [redacted] and medical examination and hematologic laboratory tests to evaluate the hematologic and molecular response, will also be performed based on published recommendations and routine clinical practice, and will be documented.

Dose adjustment and interruption or discontinuation of therapy should be performed according to the summary of product characteristics and based on the individual situation in each case (and at the discretion of the investigator), and will be reported if documented.

5.3.3 End of observation

Each patient should be followed over a period of up to 48 months. A premature termination should be documented using an electronic documentation form, specifying the date and reason for termination.

5.4 Drug

Nilotinib (Tasigna®) should be administered in line with the SPC and in accordance with the routine clinical practice, also considering recommendations of updated guidelines ELN (Baccarani *et al.*, 2009) and updated recommendations (Valent *et al.*, 2011) if applicable. The patients will be treated with commercially available products on prescription.

Information on the dosage, safety precautions, preventive measures, combination therapy and compatibilities with other medicinal products can be found in the enclosed SPC.

5.4.1 Method and route of administration

The recommended nilotinib dosing regimen is 300 mg bid for newly-diagnosed patients or 400 mg bid in second-line therapy, respectively. Nilotinib should be taken according to the SPC.

5.4.2 Observation time period

Each patient is scheduled for an observation period of up to 4 years. Therapy with nilotinib in the recommended dose will be continued until severe toxicity appears or until the physician decides to terminate it. Should therapy with nilotinib be terminated for any reason, the date of the last dose and the main reason should be documented.

5.4.3 Dosage adjustment due to toxicity

In the case of toxicity, dosage adjustment or termination of therapy can be carried out according to the SPC and updated recommendations (Valent *et al.*, 2011, Kim *et al*., 2012).

5.5 Documents

Study documents include the study contract, patient information sheet and the informed consent form (the patient receives a copy, the original goes to the study doctor), this observation plan as well as documentation guidelines. The SPC is enclosed.

5.6 Study logistics

Study documentation will be provided by the sponsor's employees. Any advertising activities

relating to the drug studied in this NIS, temporarily or conceptually linked to study-related activities by field sales representatives, are inadmissible. The physician is free to decide on whether to participate or not, any form of coercion against the physician is inadmissible. The physician will autonomously make a responsible decision to prescribe the drug based solely on therapeutic indication.

The treating physician will document follow-up visits exclusively in an electronic form via the internet using the study's electronic Case Report Form ([redacted]).

5.7 Service Remuneration

Service remuneration for informing the patient about this NIS, undertaking complete documentation and immediate reporting of possibly appearing AE and serious AE (within no later than 24 hours of their recognition) is compensated according to the scope of performed service. The maximum amount of service remuneration of [redacted] per completely documented observation of one patient over the course of 48 months is divided as follows:

Baseline/inclusion examination: [redacted]

Follow-up examination approximately at months 3, 6, 9, 12, 18, 24 and 36: [redacted]

Follow-up examination at month 48 or premature termination: [redacted]

6 Adverse events (AEs)

6.1 Safety monitoring

All adverse events (AEs) – including serious adverse events (SAEs) and safety endpoints (where relevant) – have to be collected and recorded in the study database, irrespective of causal association. All safety data AEs and SAEs occurring in association with exposure to a Novartis drug also have to be recorded in the Novartis safety database.

6.2 Adverse event

An adverse event is any untoward medical occurrence in a patient administered Tasigna that does not necessarily have a causal relationship with the treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of Tasigna whether or not related to the medicinal product(s).

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

Progression of disease will be collected on the Termination / End of Study CRF page. Progression of disease constitutes an adverse event only if it is considered to be causally related to therapy with Tasigna or if any critera for a serious adverse event (see section 6.2) is fulfilled due to the progression.

Drug of interest includes Tasigna and any comparator drug(s) if specified as part of the research objective, given at any time during the study. Medical conditions/diseases present before starting Tasigna are only considered adverse events if they worsen after starting Tasigna.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events case report/case record form (CRF) with the following information:

1. the severity grade (grade 1-4)
2. its relationship to the drug(s) of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

In addition, all reports of the following special scenarios are also considered an adverse event irrespective if a clinical event has occurred:

- Drug-drug or drug-food interaction, with or without clinical symptoms

- Drug exposure during pregnancy (via the mother or father with or without outcome) see section 6.3,
- Drug use during lactation or breast-feeding,
- Lack of efficacy, with or without clinical symptoms
- Overdose, with or without clinical symptoms
- Drug abuse and misuse, with or without clinical symptoms
- Drug maladministration or accidental exposure,
- Occupational exposure
- Dispensing errors / Medication errors, with or without clinical symptoms
- Withdrawal or rebound symptoms, with or without clinical symptoms
- Unexpected beneficial effect

Any treatment of any adverse event should be recorded on the Adverse Event CRF. Some examples of treatment to be recorded are: no action taken (i.e., further observation only); Tasigna dosage adjusted/temporarily interrupted; Tasigna permanently discontinued due to this adverse event; treatment medication adjusted; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged.

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

Information about common adverse effects already known about Tasigna can be found in the Summary of Product Characteristics (SPC). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

Information on all AEs is included in the individual patient e-CRF which is updated and committed in the study database following each patient visit.

6.3 Serious adverse event reporting

A serious adverse event (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 Tasigna
    - 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 e.g. may require 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
- transmission of infectious agent via medicinal product

For Tasigna some events are of special interest for targeted follow-up. If necessary, questionnaires will be forwarded to the relevant physicians.

To ensure patient safety, every SAE, regardless of causality assessment, 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 Tasigna 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 treating physician or other involved health care professional suspects a causal relationship to Tasigna.

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 treating physician or other involved health care professional 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 treating physician or other involved health care professional must assess the relationship to Tasigna, complete the SAE Report Form and send the completed, signed form electronically in the system within 24 hours to the local Novartis Drug Safety & Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of DS&E, specific to the site, are listed in the treating physician or other involved health care health care professional 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. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Package Insert a local DS&E department associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

6.4 Pregnancies

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

Pregnancy should be recorded on a Pregnancy Form and reported by the treating physician or other involved health care professional to the local Novartis DS&E department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis drug of interest of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took Tasigna in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

7 Ethics

7.1 Review by the Ethics Committee and Health Authority

Prior to the start of the study, the NIS will be submitted for review by an Ethics Committee. Prior to the initiation of its conduct, the NIS will be forwarded for review/notification to a relevant competent authority (in Austria to the Medicines Market Surveillance [*Medizinmarktaufsicht* / *Bundesamt für Sicherheit im Gesundheitswesen]*), in Germany to the BfArM.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Patients must be informed accordingly, and will be asked to give their consent on data-handling procedures in accordance with national regulations in place in each participating country.

7.2 Patient Information Sheet and Informed Consent Form

Prior to being enrolled in the NIS, the treating physician should provide each patient with information on the goals of the NIS, type and scope of documentation as well as on the applicable provisions on data protection. Since this NIS involves observation of an already approved drug, special patient information beyond the scope of the SPC is not required.

7.3 Data protection

Data protection and privacy regulations will be performed in capturing, forwarding, processing, and storing patient data. Patients must be informed accordingly, and will be asked to give their consent on data-handling procedures in accordance with national regulations in place in each of the countries included in the study. Each patient's data collected in the NIS will be stored under an assigned unique patient identification number which does not contain any reference to the patient's identity. Even if the study results should be published, personal data may only be used in an anonymized form.

Medical personnel responsible for the transfer of data from the patient files should be informed about their legal responsibility to safeguard data protection.

8 Legal and regulatory provisions, duty of disclosure

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well being of patients participating in non-interventional studies are protected; consistent with the principles that have their origin in the Declaration of Helsinki; and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke, et al 2008), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (European Medicines Agency 2010).

9 Data management

9.1 Data management plan

All quality assurance measures of the data management plan are contained in a project-specific data management plan (DMP) and specified for individual data management phases:

- Plausibility control during data compilation
- Data query plan with a catalog of questions leading to queries directed to the study center
- Ensuring data integrity by documented database lock

All data management processes rest on the SOP issued by the authorized CRO.

9.2 Data compilation and data query

The treating physician records entries exclusively online into the study's eCRF ([redacted] The validated eCRF web application is located on a secure server of the authorized CRO.

10 Monitoring / Site management

In study centers, site management will be conducted under safeguarding of the applicable data protection legal provisions to ensure confidentiality of patients' personal data. The goals of site management are:

- Review of the existence of written patient consent forms
- Data consistency with SDV will be checked at least once annually at each study site.
- A monitoring plan according to the respective Novartis SOP.

The Novartis data management or designated CRO will assure database auditing. An audit review of data contained upon source documents and CRFs vs. that entered into the study database will occur (data auditing).

11 Statistical analysis plan (SAP)

There are no predefined hypotheses regarding the incidence of specific safety outcomes or treatment practices. Descriptive statistical methods will be used for all variables of evaluation. All variables will be presented descriptive and will be interpreted in comparison to historic controls and published data.

Prior to database lock and statistical evaluation of the NIS, the CRO will devise a detailed SAP which will:

- specify the statistical database forming the basis for the assessment, including all adjustments, conversions and the computation of derived quantities
- establish in detail the definition of the assessment groups
- specify the statistical methods
- specify the documentation of the results

11.1 Statistical assessment rationale

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Summaries will be presented together with estimates and corresponding 95% confidence intervals (CI) as appropriate. All variables collected in this NIS will be evaluated with appropriate statistical methods and reported upon. Additional exploratory descriptive analyses of the data will be conducted as deemed appropriate, e.g. in comparison to historic controls. Due to the design of this observational study, no confirmatory statements can be derived and all statistical test results have to be interpreted as exploratory. Further details on analysis and data presentation will be specified in a separate statistical analysis plan.

11.2 Descriptive statistical methods

Quantitative variables will be described in terms of mean, standard deviation, median, quartiles and range, and qualitative variables in terms of the absolute frequency and percentage in each category. The 95% confidence intervals will be presented.

Descriptive statistics will be used to summarize all safety outcomes. No formal hypothesis testing or statistical significance testing is planned. Incidence rates of SAEs, AEs and SAEs/AEs (to be defined in the SAP) will be estimated. The AEs of special interest that will be included in this analysis are specified in the nilotinib SPC. Point estimates for the incidences of those AEs as well as two-sided 95% confidence intervals will be provided. Incidence is calculated as the number of patients with occurrence of a specific event during the safety observation period, divided by the total number of patients observed in the study period, multiplied by 100. In addition, incidence rate per 100 patient years is calculated as the number of events occurring during the safety observation period, divided by the total number of patient-years of the safety observation period, multiplied by 100. Time-to-event data and survival analyses will be conducted using the Kaplan-Meier method. Derivation and censoring of these time-to-event data is described in the SAP.

11.3 Analysis population and methods

The analysis will include all patients who have received at least one dose of nilotinib and for whom at least one follow-up record exists.

Safety

Data related to safety (e.g. cardiovascular) and all AEs are presented in the form of frequency tables; AEs (severe and non-severe), which are related to nilotinib, are also summarized in the form of frequency tables.

Efficacy

Therapeutic response is evaluated using the latest published version of the ELN recommendations (Baccarani et al. 2009 or later).

11.4 Missing values and discontinuation of therapy

The SAP will contain a description and justification of the management of missing values, including statistical methods to handle therapy discontinuation.

11.5 Analysis sets

The analysis is based on a patient population with documented administration/prescription of nilotinib for whom at least one in-therapy follow-up is available.

11.6 Analysis software

The statistical analysis is conducted with SPSS® and/or SAS® in their most recent versions.

11.7 Interim analyses

No formal interim analyses will be performed. However, descriptive summaries will be prepared annually, for the purposes of reporting Health Authorities.

11.8 Determination of sample size

According to the study design, no formal sample size estimate with respect to statistical tests of hypotheses is applicable.

The sample size of 100 patients has been determined on practical considerations and availability of patients. This sample size will be sufficient to to have about 80% probability of observing at least one adverse event which has an incidence of 1.5%, and 95% probability of observing at least one adverse event which has an incidence of 3%.

12 Final report and publication

The sponsor of the project Novartis and the medical director are responsible for submitting the final report to the HA in due time following completion of the statistical analysis. Study results will be jointly published. Before the medical director of the study publishes it, Novartis reserves the right to comment on the manuscript/abstract.

13 Documentation and archiving

The sponsor is responsible for keeping the study documentation in the archives for at least 10 years.

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