NOVARTIS

Clinical Development

AMN107 (Nilotinib, Tasigna)

CAMN107ECN02E1 / NCT02272777

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

RAP Module 3 – Detailed Statistical Methodology

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Document History – Changes compared to previous version of RAP module 3

Version	Date	Changes
1.0	21-Apr-2015	Final version 1.0
2.0	Dec.2016	Updated to add Hepatitis B testing results.
3.0	Mar.2017	Updated the sample size 234 and delete “important” from DV table.
4.0	Jan.2019	Add exposure analysis for section 1.5.

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1 Statistical methods planned in the protocol and determination of sample size

Data will be analyzed by Novartis or designee using SAS® version 9.2 or higher (SAS Institute Inc., Cary, NC, USA) according to the data analysis Section 10 of the study Protocol.

1.1 Statistical and analytical plans

Summary tables will be provided for patient disposition, protocol deviation, and safety data. The data will also be listed.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented, unless otherwise stated.

1.2 Subjects and treatments

1.2.1 Analysis sets

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

Safety Set

The Safety Set consists of all patients who received at least one dose of study medication. The statement that a patient had no AE (on Adverse Event CRF page) constitutes a safety assessment. Patients will be analyzed according to the study treatment they actually received at the beginning the extension study.

1.2.2 Treatments

Study treatments are: nilotinib (AMN107, Tasigna) and imatinib (STI571, Glivec). In this study patient will continue treatment of the drug (imatinib or nilotinib) which they are taking at the end of CAMN107ECN02.

1.3 Patient demographics and other baseline characteristics

Demographics at the enrollment will be listed for all patients.

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

1.3.1 Patient disposition

The number of patients completed the study as well as the primary reason for early discontinuation will be summarized.

1.3.2 Protocol deviation

Patients with following protocol deviations will be listed:

1. Inclusion Criteria/Exclusion Criteria: the subject was entered in the trial, but did not meet the eligibility for one or more of the Inclusion or Exclusion criteria defined in the protocol
2. Study Drug Administration: the subject did not take the study drug as per protocol
3. Discontinuation Criteria: the subject met criteria defined in the protocol for discontinuation but was not discontinued from study
4. Prohibited Concomitant Medication: the subject took prohibited concomitant medication as defined in the protocol

1.4 Efficacy evaluation

Not applicable to this study.

1.5 Safety evaluation

Treatment exposure is defined as last dose date minus start date of study drug + 1, actual dose intensity is defined as total dose/treatment exposure, relative dose intensity is defined as actual dose intensity/assigned total daily dose (600 mg). All these variables will be summarized using descriptive statistics (N, mean, standard deviation, minimum, median and maximum). And actual dose intensity category will be summarized using frequency counts and percentages.

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

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be listed by patient and those collected during pre-study period are to be flagged. The incidence of AE will be summarized by system organ class (SOC) and or preferred term (PT), severity (based on CTCAE v3.0, the same one applied in the core study), and relation to study drug. Note that AEs from pre-study will not be analyzed (see section 1.8).

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by SOC, PT and treatment.

The result of Hepatitis B testing will be summarized and listed.

For all safety analyses, the Safety Set will be used. All listings and tables will be presented according to the treatment actually taken.

1.6 Other topics

Urine pregnancy test results for female patients will be listed.

1.7 Determination of sample size

The sample size of this study is not based on statistical consideration. Patients that completed the study of CAMN107ECN02 will be screened for eligibilities to enter this extension study. The upper bound of the sample size of this extension study is 234, the number of patients who completed study of CAMN107ECN02.

1.8 Changes from protocol specified analyses

In protocol section 8.1 it specified that conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. However due to the roll-over feature of the study the CRF did not include a Medical History page, these continuing conditions were recorded in Adverse Event page, and could be identified by the comparing the start date of AE with the informed consent date of the patient, e.g AEs with a start date before informed consent are pre-study AEs and will not be included into analysis. These 'AEs' are to be flagged in the AE listing.

SIGNATURE PAGE

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