U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #: **Supplement #:**	022068 S-27
Drug Name:	TASIGNA® (AMN107/nilotinib)
Indication(s):	Ph+ CML
Applicant:	NOVARTIS
Stamp Date: **Primary Review Date:** **PDUFA Date:**	25-SEPT-2017 14-FEB-2018 25-MARCH-2017
Review Priority:	Priority
Biometrics Division:	DB V / CDER
Statistical Reviewer:	Dr. Kallappa M. Koti
Concurring Reviewers:	Dr. Lei Nie, Team Leader Dr. Thomas Gwise, Deputy Division Director Division of Biometrics V
Medical Division:	DHP
Clinical Team:	Dr. Nicholas Richardson Dr. Angelo De Claro, CDTL
Project Manager:	Ms Natasha Kormanik

1. Introduction

Novartis Pharmaceuticals Corporation has submitted this supplemental New Drug Application (sNDA) for Tasigna® (nilotinib) oral capsules. Novartis provides the Agency with all outstanding components outlines in the Written Request (WR) issued for Tasigna and to request a pediatric exclusivity determination. Novartis also seeks approval of Tasigna (50 mg oral capsule) for the treatment of pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) based on the results from two Tasigna pediatric studies, CAMN107A2120 and CAMN107A2203.

- Study CAMN107A2120 ("Study 1"): a Phase I, open-label, multi-center study evaluating the pharmacokinetics (PK), safety, and preliminary efficacy of nilotinib at a dose of 230 mg/m2 twice daily in pediatric patients with Ph+ CML resistant or intolerant to imatinib or dasatinib or refractory/relapsed Ph+ acute lymphoid leukemia. The study is completed.

- Study CAMN107A2203 ("Study 2"): a Phase II, open-label, multi-center study evaluating the efficacy and safety of nilotinib 230 mg/m2 twice daily conducted in Ph+ CML-CP newly diagnosed and Ph+ CML-CP pediatric patients resistant or intolerant to imatinib or dasatinib. At the time of the data cut-off of the primary analysis (01-Jun-2016), all patients had completed at least 12 cycles of 28 days of treatment or discontinued early. The study is ongoing and will continue for a total of 66 cycles.

The details of the designs for studies A2120 and A2203 were discussed and agreed with the Agency. FDA issued a Written Request (WR) on 19-Jun-2009 that was subsequently revised on 07-Mar-2014 as Amendment 1. The current WR lists Study CAMN107A2120 as Study 1 and Study CAMN107A2203 as Study 2.

An overview is provided in Table 1 below.

Table 1: Overview of the studies and their status

Study	Study design	Number of patients included in the analyses	FPFV*/LPLV Status
A2203	Phase II, open-label multi-center study evaluating efficacy and safety of nilotinib 230 mg/m^2 in pediatric patients with newly diagnosed Ph+ CML-CP, or imatinib/dasatinib-resistant/intolerant Ph+ CML-CP or AP	Total: 58 patients Resistant/intolerant CML-CP: 33 Newly diagnosed CML-CP: 25	20-Aug-2013 01-Jun-2016 Ongoing; All patients had completed 12×28 day cycles or discontinued
A2120	Phase I open-label multi-center study evaluating PK, PD, safety, and preliminary efficacy of nilotinib 230 mg/m^2 in pediatric patients with newly diagnosed Ph+ CML-CP, imatinib/dasatinib-resistant/intolerant Ph+ CML-CP or AP or refractory/relapsed Ph+ ALL	Total: 15 patients Resistant/intolerant CML-CP: 11 Relapsed/refractory ALL: 4	14-Apr-2011 01-Jul-2015 Completed
CP = chronic phase; AP = accelerated phase; AL = acute lymphoblastic leukemia * FPFV = first patient first visit; LPLV = last patient last visit			

Study CAMN107A2120 was a dose escalation, safety, tolerability, pharmacokinetic (PK) study. No further discussion of this study is provided in this review.

2. Study CAMN107A2203

This study is used to support the efficacy. The primary objective was to assess the efficacy of nilotinib in each of the three patient cohorts:

Cohort 1: CML-CP resistant or intolerant to imatinib or dasatinib
Cohort 2: CML-AP resistant or intolerant to imatinib or dasatinib
Cohort 3: Newly-diagnosed CML-CP in chronic phase

A total of 58 patients received nilotinib treatment in this study: 33 patients with resistant or intolerant CML-CP, and 25 patients with newly-diagnosed with CML-CP. No patients were enrolled in Cohort 2. There were 34 males and 24 females whose age ranged from 2 years to 17 years. Median age was 13 years.

3. The primary endpoint in Study A2203

Molecular response is a well-established endpoint in CML, and was assessed by determining the level of BCR-ABL transcript in peripheral blood samples. Molecular response is calculated as the percent ratio of BCR-ABL transcripts versus ABL transcript (control gene) converted to a reference standard according to the International Scale (IS). Major molecular response (MMR) is defined as a value of ≤0.1% of BCR-ABL/ABL ratio on the IS, and corresponds to a ≥3 log reduction of BCR-ABL transcripts from a standardized baseline value for untreated CML.

The other efficacy endpoints included molecular, cytogenetic, and hematological response rates, time to response, duration of response, time to disease progression, and overall survival.

4. Efficacy Results

Efficacy is evaluated in Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP. Efficacy data from patients with CML-CP from Study A2203 and Study A2120 were pooled. The efficacy analyses were performed separately for the resistant/intolerant CML-CP and the newly diagnosed CML-CP patient populations. *All efficacy endpoints were analyzed descriptively; no hypothesis testing was performed. There were no formal sample size calculations.*

A total of 69 pediatric patients (from 2 to less than 18 years of age) with either newly diagnosed Ph+ CML-CP (n=25) or imatinib/dasatinib resistant or intolerant Ph+ CML-CP (n=44) received nilotinib treatment at a dose of 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg). The following efficacy statements are verified to be correct.

- In patients with resistant or intolerant CML, the major molecular response (MMR; BCR-ABL/ABL ≤0.1% IS) rate was 40.9% (95% CI: 26.3%, 56.8%) at 12 cycles (28 days per cycle), with 18 patients being in MMR.

- In patients with newly diagnosed CML, the MMR rate was 60.0% (95% CI: 38.7%, 78.9%) at 12 cycles, with 15 patients achieving MMR.

- In patients with resistant or intolerant CML, the cumulative MMR rate was 47.7% (95% CI: 32.9%, 62.5%) by cycle 12. In newly diagnosed CML patients, the cumulative MMR rate was 64.0% (95% CI: 45.2%, 82.8%) by cycle 12.

- Among the 21 patients with resistant or intolerant CML who were in MMR at any time on treatment, the median time to first MMR was 2.76 months (95% CI: 0.03, 5.55).

- For the 17 newly diagnosed CML patients who achieved MMR, the median time to first MMR was 5.55 months (95% CI: 5.52, 5.75).

5. Conclusion

WR to conduct two studies is complied.

Kallappa M. Koti, Ph. D.
Mathematical Statistician

Cc:
HFD-109/Mr. Natasha Kormanik
HFD-107/Dr. Dr. Nicholas Richardson, Dr. Angelo De Claro
HFD-711/Dr. Lei Nie, Dr. Thomas Gwise
HFD-700/Ms. Lillian Patrician

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KALLAPPA M KOTI
02/14/2018

LEI NIE
02/14/2018

THOMAS E GWISE
02/28/2018