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*APPLICATION NUMBER:*

**22-068**

**MEDICAL REVIEW**

## CLINICAL REVIEW

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Established Name	Nilotinib
(Proposed) Trade Name	Tasigna
Therapeutic Class	Antineoplastic
Applicant	Novartis
Priority Designation	Standard
Formulation	Capsules
Dosing Regimen	Oral
Indication	chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant or intolerant to prior therapy including imatinib

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## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

The reviewers recommend subpart H (accelerated) approval of nilotinib for use in the treatment of adults with chronic phase (CML-CP) and accelerated phase (CML-AP) chronic myeloid leukemia (CML) patients with resistance or intolerance to prior therapy including imatinib mesylate.

Patients with CML that is resistant to imatinib or who can not tolerate imatinib have limited therapeutic options, although dasatinib has also received accelerated approval for these indications. The clinical data presented in the NDA provide substantial evidence of effectiveness of nilotinib in the form of hematologic responses in the CML-AP population and cytogenetic responses in the CML-CP population which appear to be durable. Final characterization of this durability will require a longer follow-up period. This follow-up data could potentially be the basis for regular approval. The safety profile of dasatinib is acceptable, given the serious life-threatening nature of these disease entities. Since nilotinib prolongs the QT interval and has resulted in sudden deaths, the reviewers recommend a black box warning regarding sudden deaths and QT interval prolongation to be included in the label and the applicant has agreed to a black box warning.

### **1.2 Recommendation on Post-marketing Actions**

#### **1.2.1 Risk Management Activity**

This drug will be prescribed by physicians familiar with the management of toxicity associated with the use of anti-neoplastic agents. A black box warning describing the risk of sudden death and QT interval prolongation will be included in the label. Drug-drug interactions are seen with nilotinib and will be described in the labeling. The applicant will conduct post-marketing pharmacovigilance activities to evaluate safety signals associated with nilotinib including QT interval prolongation.

#### **1.2.2 Required Phase 4 Commitments**

The reviewers recommend the following commitment under subpart H (accelerated approval) :

To submit the complete study report (at least 24 months follow-up in all patients) and data from study 2101, a phase 2 multi-center study of nilotinib in patients with imatinib resistant or intolerant chronic myeloid leukemia.

### 1.2.3 Other Phase 4 Requests

The following additional post-marketing commitments are recommended:

To submit the completed report and datasets for the hepatic impairment study.

To submit the completed report and datasets for the absolute bioavailability study.

To conduct clinical study(ies) to evaluate if multiple doses of nilotinib alter the metabolism of a sensitive CYP2C9 substrate (for example, S-warfarin). If a significant interaction is demonstrated, additional clinical studies to evaluate if multiple doses of nilotinib alter the metabolism of a sensitive CYP2C8 substrate (for example, repaglinide) and/or a sensitive CYP3A4 substrate (for example, midazolam) may be needed.

To conduct a clinical study to evaluate if H2 blockers/proton pump inhibitors alter the pharmacokinetics of nilotinib.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Nilotinib is an inhibitor of tyrosine kinases including BCR-ABL, the molecular hallmark of CML. It is orally administered at 400 mg twice a day at least two hours after taking food. Nilotinib was evaluated for the treatment of adult patients with CML-chronic phase (CML-CP) and CML-accelerated phase (CML-AP) who were resistant to or intolerant of prior imatinib therapy.

Efficacy and safety data were generated from a single open-label, multi-center Phase 1/2 study. The study has several treatment arms, but only two treatment arms provide the relevant efficacy data to support the proposed indication. There were 280 patients with CML-CP and 105 patients with CML-AP with efficacy data provided as of the cut-off date for the 120-day safety update provided during the NDA review. The safety database included 318 patients with CML-CP and 120 patients with CML-AP and included patients treated in the Phase 1 dose escalation portion of the study.

The median duration of nilotinib treatment was 8.7 months for CML-CP patients and 5.6 months for CML-AP patients.

### 1.3.2 Efficacy

Evidence of nilotinib efficacy is based on the results of a single Phase 2 study with two populations studied, CML-CP and CML-AP. The primary efficacy endpoint in the CML-CP population was major cytogenetic response rate (MCyR), defined as elimination or diminution to less than 35% of Ph<sup>+</sup> hematopoietic cells. According to the protocol, the primary efficacy endpoint in CML-AP was overall hematologic response rate which included complete hematologic response (CHR) or no evidence of leukemia (NEL) and return to chronic phase (RTC). *The reviewers consider CHR and NEL (a major hematologic response) as surrogates reasonably likely to predict clinical effectiveness for accelerated approval for the CML-CP indication. However, we do not consider RTC as a surrogate reasonably likely to predict clinical benefit. Therefore, FDA reviewers recommend presentation of the hematologic response data for the CML-AP population based on CHR and NEL only.*

#### Primary efficacy endpoints

CML-CP: A total of 92 of 232 (40%) evaluable patients achieved an unconfirmed MCyR (95% CI: 33, 46). This included a 28% complete cytogenetic response rate and a 12% partial response rate. Fifty-nine percent of CML-CP patients with a major cytogenetic response had a duration of response of at least 6 months.

CML-AP: The major hematologic response (MHR) which included complete hematologic response and no evidence of leukemia/marrow response rate (CHR + NEL) was 26% (27 / 105) with a (95% CI: 18, 35). Sixty-three percent of CML-AP patients with a confirmed hematologic response had a duration of response of at least 6 months.

#### Secondary efficacy endpoints

CML-CP: Complete hematologic response was observed in 92 patients (50%) of the 185 patients in the primary and additional population who were without CHR at baseline and therefore assessable for CHR. The median time to CHR for the 92 patients without a CHR at baseline of the 280 patients with at least 6 months of follow-up was 1.0 months. Median duration was not reached. The longest duration of CHR seen was 15.6 months.

CML-AP: An unconfirmed MCyR was seen in 21% of the 81 evaluable patients and confirmed MCyR in 6% of patients. The longest duration of response seen was 13.6 months. The median time to MCyR was 2.8 months. Two out of the 17 patients had a loss of MCyR.

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### Subgroup Analyses:

In the single study, approximately 30% of patients were 65 or over.

CML-CP: There was no difference in major cytogenetic response rate between patients aged < 65 years and those  $\geq$  65 years. Female patients had a similar response rate (47/92, 51.1%) to male patients (45/93, 48.9%). Most of the responders were of Caucasian race (85/92, 92%).

CML-AP: The major hematologic response was higher in patients < 65 years of age (22/72, 31%) than in patients  $\geq$  65 years (5/33, 15%). The response rate was slightly higher in males (14/26, 54%) than females (12/26, 46%).

### Limitations of Data

Efficacy was based on a single clinical trial only with two groups of CML, CML-CP and CML-AP. There was no comparator arm because it was deemed that no effective control therapy was available.

The efficacy conclusions are based on interim data from an ongoing study. There were two cut-off dates for the primary and additional patient analyses. The number of additional patients were greater than the number in the primary analysis submitted in the initial NDA submission in the CML-CP population. All CML-CP patients had at least a 6-month follow-up and all CML-AP patients had at least a 4-month follow-up. These follow-up periods were sufficient for evaluation of response rates, but not for complete evaluation of durations of responses.

The efficacy endpoints were not assessed by an independent review team which could be subject to bias.

The protocol specified the use of FISH analysis when bone marrow cytogenetics were not available. FISH is not a validated test and only bone marrow cytogenetics were deemed assessable for major cytogenetic response for CML-CP population in this submission for accelerated approval. Response rates by bone marrow cytogenetics were considered a surrogate endpoint reasonably likely to predict clinical benefit for accelerated approval.

The protocol specified primary efficacy endpoint in CML-AP was overall hematologic response which included complete hematologic response (CHR) or no evidence of leukemia (NEL) and return to chronic phase. Only CHR and NEL (a major hematologic response) were considered as surrogates reasonably likely to predict clinical benefit for accelerated approval.

### Efficacy Conclusions

The efficacy data demonstrate that nilotinib treatment results in cytogenetic and hematologic responses in patients with CML-CP and CML-AP who are imatinib-resistant or intolerant on imatinib. Most responses occurred within 3 months of initiation of therapy. The number of

patients in the population who received prior dasatinib and imatinib were too small for interpretation. There were only slight age and gender-related response differences apparent in both the CML-CP and CML-AP populations except for hematologic response in the AP population, which seemed to be higher in patients less than 65 years of age.

The trial was conducted per protocol except for certain eligibility criteria. The trial appears to have been well conducted. The largest accruing groups and those with the most responses were not found to have potentially confounding deficiencies on FDA site inspection.

The results of the trial provide evidence that nilotinib is effective as a single agent in CML-CP and CML-AP groups who are imatinib-resistant or –intolerant to prior imatinib. The primary analysis is conservative, since patients who were not assessable for response were counted as non-responders.

Cytogenetic and hematologic responses in imatinib resistant or intolerant CML-CP and CML-AP patients respectively, who have limited treatment options, are reasonably likely to predict clinical benefit and therefore support accelerated approval.

### 1.3.3 Safety

Four hundred and thirty eight patients comprised the safety population including 318 patients with CML-CP and 120 patients with CML-AP. All patients were treated with a starting dose of 400 mg orally twice daily.

The median duration of exposure to nilotinib in CML-CP patients was 245 days. Fifty-two percent were treated for 6 - 12 months, while 19% were treated for less than 3 months and 20% were treated for more than 12 months.

The median duration of exposure to nilotinib in CML-AP patients was 138 days. Thirty-five percent were treated for 6 - 12 months, while 23% were treated for less than 3 months and 11% were treated for more than 12 months.

In CML-CP patients, the most commonly reported drug-related adverse reactions (>10%) were rash, pruritis, nausea, fatigue, headache, constipation, diarrhea and vomiting. The common serious drug-related adverse reactions were thrombocytopenia and neutropenia.

In CML-AP patients, the most commonly reported drug-related adverse reactions (>10%) were rash, pruritus and constipation. The common serious drug-related adverse reactions were thrombocytopenia, neutropenia, pneumonia, febrile neutropenia, leukopenia, intracranial hemorrhage, elevated lipase and pyrexia.

Treatment-emergent grade 3/4 thrombocytopenia occurred in 28% of CML-CP patients and 37% of CML-AP patients. Grade 3/4 neutropenia occurred in 28% of CML-CP patients and 37% of

CML-AP patients. Grade 3/4 anemia occurred in 8% of CML-CP patients and 28% of CML-CP patients.

Other treatment-emergent grade 3/4 laboratory abnormalities occurring in CML patients receiving nilotinib included:

*greater than 5% incidence* : elevated lipase, hyperglycemia, hypophosphatemia, elevated bilirubin

*less than 5%* : elevated SGOT or SGPT, hyperkalemia, hyponatremia, hypokalemia, decreased albumin, hypocalcemia, elevated alkaline phosphatase, and elevated creatinine

A relatively high number of patients experienced QTcF prolongations from baseline of > 30 msec (33.0% of CML-CP patients, 40.8% of CML-AP patients). QTcF increases of > 60 msec were reported in 1.9% of CML-CP and 2.5% of CML-AP patients. The incidence of absolute QTcF values > 500 msec was < 1%. There were ten sudden deaths reported. Six sudden deaths occurred in the ongoing phase 1/2 study (an additional death was reported after database lock but appeared to be possibly related to cardiac surgery and other moribidity) ; 4 deaths occurred in the expanded access program or with single patient use. Syncope occurred in 2% of CML-CP and 2.5 % of CML-AP patients.

The following wording is recommended for the black box warning:

**Tassigna prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib. Tassigna should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to Tassigna administration and should be periodically monitored. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided. Patients should avoid food 2 hours before and 1 hour after taking dose. Use with caution in patients with hepatic impairment. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.**

#### 1.3.4 Dosing Regimen and Administration

Nilotinib is dosed at 400 mg orally taken twice daily. The capsules should be swallowed whole with water. No food should be consumed for at least 2 hours before the dose is taken and no food should be consumed for at least one hour after. Treatment — continue until — unacceptable toxicity occurs. Treatment is recommended in adults only.

Dose reductions may be made to 400 mg orally once daily for hematologic and non-hematologic toxicities, drug interactions and dose adjustments.

### 1.3.5 Drug-Drug Interactions

#### Effects of Nilotinib on Drug Metabolizing Enzymes and Drug Transport Systems

Nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 in vitro, potentially increasing the concentrations of drugs eliminated by these enzymes. In addition, single-dose administration of Tassigna with midazolam (a CYP3A substrate) to healthy subjects increased midazolam exposure by 30%. Caution should be exercised when co-administering Tassigna with substrates for these enzymes that have a narrow therapeutic index. Since warfarin is metabolized by CYP2C9 and CYP3A4 it should be avoided if possible. In vitro studies also suggest that nilotinib may induce CYP2B6, CYP2C8 and CYP2C9, and thereby has the potential to decrease the concentrations of drugs which are eliminated by these enzymes.

Nilotinib inhibits human P-glycoprotein. If Tassigna is administered with drugs that are substrates of Pgp, increased concentrations of the substrate drug are likely, and caution should be exercised.

#### Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes

Nilotinib undergoes metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 can increase or decrease nilotinib concentrations significantly.

**Ketoconazole:** In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at 400 mg once daily for 6 days, systemic exposure (AUC) to nilotinib was increased approximately 3-fold.

**Rifampicin:** In healthy subjects receiving the CYP3A4 inducer, rifampicin, at 600 mg daily for 12 days, systemic exposure (AUC) to nilotinib was decreased approximately 80%.

#### Drugs that Inhibit Drug Transport Systems

Nilotinib is a substrate of the efflux transporter P-glycoprotein (Pgp, ABCB1). If nilotinib is administered with drugs that inhibit Pgp, increased concentrations of nilotinib are likely, and caution should be exercised.

### 1.3.6 Special Populations

No age- or gender-related differences in the safety of nilotinib were apparent between adult patients ages 65 and older and patients less than 65 years of age. Nilotinib has not been evaluated in children.

No conclusions can be made on any race-related differences in efficacy or safety of nilotinib, because fewer than 10% of patients in clinical studies were non-Caucasian.

A study evaluating the use of nilotinib in a population with hepatic impairment is ongoing. Data from this study was not provided with this application.

The available data indicate that renal elimination plays a minor role in the clearance of nilotinib. Nilotinib has not been studied in patients with renal impairment.

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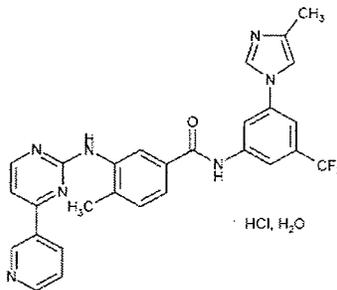
## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Nilotinib (AMN107), a synthetic aminopyrimidine, is a highly selective inhibitor of the kinase activity of the Bcr-Abl oncoprotein. This protein is the product of the BCR-ABL fusion gene, which results from a reciprocal chromosomal translocation in a bone marrow hematopoietic stem cell. Nilotinib is an inhibitor of the Abl tyrosine kinase activity of the Bcr-Abl oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukemia cells. The drug binds tightly to the inactive conformation of the kinase domain in such a manner that it is an inhibitor of wild-type Bcr-Abl and maintains activity against 32/33 imatinib-resistant mutant forms of Bcr-Abl.

Established name: Nilotinib (AMN107)

#### Chemical structure of AMN107



4-Methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide, monohydrochloride, monohydrate

Proposed trade name: Tassigna®

Chemical class: Bcr-Abl tyrosine kinase inhibitor

Pharmacological class: Aminopyrimidine

Proposed indication: Chronic Myelogenous Leukemia resistant to or intolerant of imatinib mesylate

Dosing regimen: 400 mg orally twice daily

## 2.2 Currently Available Treatment for Indications

Dasatinib (Sprycel®) received accelerated approval in June 2006 for use in the treatment of adults with chronic phase (CP), accelerated phase (AP), or myeloid or lymphoid blast (MB or LB) phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib mesylate.

## 2.3 Availability of Proposed Active Ingredient in the United States

Nilotinib is not currently marketed in this country. Nilotinib is available under an expanded access protocol for patients with AP- or BP CML or Ph+ ALL who are resistant to or intolerant of imatinib mesylate.

## 2.4 Important Issues With Pharmacologically Related Products

Nilotinib is pharmacologically related to imatinib mesylate (Gleevec®) and dasatinib (Sprycel®), both of which are inhibitors of Bcr-Abl tyrosine kinase.

Imatinib mesylate (Gleevec®) was approved on May 10, 2001 for the treatment of CML in three clinical settings: CML-BC, CML-AP and CML-CP [1]. The most frequently reported drug related adverse events were edema, nausea and vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash (cutaneous toxicity). A variety of adverse events represented local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. Cytopenias included neutropenia and thrombocytopenia. Severe hepatotoxicity including elevations of transaminases or bilirubin lead to liver failure or death. Post marketing safety reports included cardiotoxicity including severe congestive heart failure in ten patients [2], hypophosphatemia, with associated changes in bone and mineral metabolism [3] [4] and fatal hepatitis [5].

Dasatinib was approved on June 28, 2006 for the treatment of adult patients with imatinib resistant/intolerant CML-CP, CML-AP and Ph + ALL [6]. The most common severe toxicities associated with dasatinib were hematologic, including neutropenia thrombocytopenia and anemia. Others included neutropenic fever, bleeding events, pyrexia, dyspnea, pleural effusion, and diarrhea. Other significant less commonly occurring adverse reactions included cardiac failure, QTc prolongation and CNS hemorrhages, most of which were fatal.

## 2.5 Presubmission Regulatory Activity

April 24, 2004 Initial investigational new drug application submitted

Dec 9, 2004 End-of-phase 1 meeting for resistant CML CP, AP, BC.

In the absence of a controlled trial in the CP cohort, FDA agreed that a literature-based comparison to Interferon from large published randomized interferon studies would be reasonable.

- Sept 8, 2005 End-of-phase 2 meeting for second indication, newly diagnosed CML CP.
- Feb 13, 2006 End-of-phase 1-2 meeting follow-up meeting.

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FDA stated that its acceptability will depend on the magnitude of the benefit seen, with the duration of the response being crucial. FDA recommended that the sample size in CML-AP not be decreased.

FDA recommended presenting additional efficacy data prior to approval in order to provide additional follow-up validating the demonstration of and providing better precision about the durability of response.

- Feb 3, 2006 Agency informed of sudden deaths and clinical information amendment submitted
- Feb 27, 2006 Thorough QT study proposal submitted.
- March 20, 2006 QT e-mail regarding responses to their QT study proposal : asked justification of conducting healthy volunteer instead of patient study; told that if higher doses are not tolerated, the study will not provide information on the QT effects at the proposed clinical doses; not all subjects may achieve steady state on day 3.
- March 23, 2006 QT question e-mail we are concerned that at completion of your proposed QT study you will not have a definite answer regarding the potential for QT prolongation at the clinical doses; you may also need to perform a QT study in patients (e.g., your planned phase 3 trial) ; the sample size calculations could be based on detecting a larger change in QT (e.g., 10-15 msec).
- April 27, 2006 Orphan drug designation for nilotinib in CML granted.
- May 11, 2006 Fast Track designation for the treatment of imatinib-resistant or intolerant Ph + CML granted.

August 2006	Special Protocol Assessment for a phase 3 randomized, open-label, multi-center study of nilotinib vs imatinib in adult patients with Ph + CML in CP who have suboptimal CyR on imatinib.
August 2006	Special Protocol Assessment for GIST
Sept 21, 2006	QT study meeting
Sept 28, 2006	Re-submission SPA(s) for GIST and CML.
Sept 29, 2006	Submission of NDA 22068

*Reviewer Comment ; Post submission, the PDUFA goal date was extended to October 29, 2007 due to submission of a major amendment. The applicant was notified of the decision to extend the goal date on July 13, 2007.*

## **2.6 Other Relevant Background Information**

At the time of NDA submission, there were no regulatory actions in other countries. Subsequently, the drug has been approved in Switzerland and the EMEA for the treatment of CML.

## **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

### **3.1 CMC (and Product Microbiology, if Applicable)**

This section is excerpted from the Chemistry review by William Timmer, PhD. The reader is referred to the CMC review for further details.

The drug substance is Nilotinib hydrochloride monohydrate.

Nilotinib is 4-Methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl) phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide monohydrochloride monohydrate. Nilotinib is a yellowish to greenish-yellowish powder, and has a molecular formula of C<sub>28</sub>H<sub>22</sub>F<sub>3</sub>N<sub>7</sub>O•HCl • H<sub>2</sub>O with a corresponding molecular weight of 583.99 g/mol.

The solubility of Nilotinib in aqueous solutions decreases with increasing pH, and Nilotinib is practically insoluble in buffer solutions of pH 4.5 and higher. Nilotinib is considered a low solubility/low permeability (Class IV) compound in the BCS. Therefore, dissolution of nilotinib can potentially be the rate-limiting step for in vivo absorption.

The structure of Nilotinib is supported by both the synthetic route as well as analytical and spectroscopic analyses. Nilotinib does not have a chiral center and hence no stereochemistry.

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The synthesis of Nilotinib involves ' \_\_\_\_\_ Starting materials are commercially available or were prepared from commercially available materials. A subsequent agreement with the sponsor defined the starting materials, with the caveat that the starting materials could be appropriately controlled.

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\_\_\_\_\_ These by-products/impurities are suitably analyzed by the analytical test methods such that the quality of the drug substance is maintained.

The drug product is Tasigna® (nilotinib) Tablets.

Tasigna® (nilotinib) 200 mg hard capsules \_\_\_\_\_ dosage form for oral administration.

The analytical specifications and tests employed for the release of Tasigna (nilotinib) comply with the requirements of ICH guidelines Q3A(R), Q3C and Q6A. The sponsor has provided batch analyses for all drug product batches.

As to be expected, dissolution testing proceeded through several iterations before a final test method was developed. The method was validated for selectivity, accuracy, precision and linearity. The acceptance criteria for release and stability control (Q = \_\_\_\_\_ in 30 minutes) represents a standard requirements for \_\_\_\_\_ solid oral dosage forms.

The drug product will be marketed in the either blister packs

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Stability studies were performed in compliance with the applicable current ICH guidelines. The registration stability reports contain data from long-term and accelerated studies of three pilot and three production batches for storage up to 18 months, plus stress and photostability testing. Analysis of the stability data indicate an expiry of 24 months when stored protected from light and at a temperature no higher than 25°C.

### **3.2 Animal Pharmacology/Toxicology**

This section is excerpted from the Animal Pharmacology/Toxicology review by Shwu-Luan Lee, PhD. The reader is referred to the review for further details.

Nilotinib (AMN107) is a kinase inhibitor that targets Bcr-Abl, c-Kit and platelet derived growth factor (PDGF) receptor, via an ATP-competitive mechanism.

Orally administered nilotinib was absorbed rapidly (T<sub>max</sub> 0.5-4 hr), with bioavailability ranging from 20 to 43% in the tested rodent (mice and rats) and non-rodent (rabbits and monkeys) species. The plasma protein binding of nilotinib was high (over 97% in all tested species), and bile, uveal tract (pigment layer in the eye), stomach glandular, liver, and adrenal gland, had highest nilotinib concentration. Although nilotinib showed little penetration through the blood-brain and blood-testis barrier, it crossed the placenta and entered the fetuses. Nilotinib was found in the milk of lactating rats after a single oral dose. The biotransformation of nilotinib was primarily oxidation, oxidative cleavage of the imidazole ring, amide bond hydrolysis, and glucuronic acid conjugation. The commonly found metabolites in rat, dog, monkey and human were P20, P36, P36.5, P41.6, P42.1, P47 and P50. The rat and monkey profiles were most similar to that of human, and that in dog was the least. One of the major metabolites in human, P36.5 (approximately 7% AUC of parent drug), was also found in plasma of monkey but not other species. Cytochrome P450 (CYP) 3A4 was responsible for the hepatic oxidative clearance of nilotinib. In in vitro studies, nilotinib inhibited CYP 2D6, 2C19, 2C9, 3A4, 2C8, UGT1A1 and P-glycoprotein, but induced CYP 2B6, 2C8, 2C9, 3A4, 1A1, 1A2 and UGT1A1. The main excretion after oral doses was fecal. After repeated administration (4 to 39 weeks), while the accumulation was not seen in every dose group in rats, nilotinib accumulated in dogs (in both sexes at higher doses) and monkeys (in both sexes at all doses tested). The systemic exposure to nilotinib increased with dose, and was generally proportional in rats, but less than proportional in dogs and monkeys.

#### **Pharmacologic activity**

The inhibitory effects of nilotinib to the target tyrosine kinases (Bcr-Abl fusion protein, c-Kit and PDGFR $\alpha$  and PDGFR $\beta$ ), as well as selected Bcr-Abl mutants, were characterized in in vitro and/or in vivo systems. Nilotinib inhibited the cellular activities in 32 out of 33 mutants tested. The Bcr-Abl mutants including E255K, G250E and Y253H, are commonly identified in CML patients who were relapsed from or resistant to imatinib treatment. Nilotinib, however, exhibited no effects against mutant T315I, a mutant resistant to both imatinib and dasatinib.

Nilotinib (10  $\mu$ M) inhibited the JAKs (Janus kinases) dependent cell proliferation (20-60%), indicating the link between Bcr-Abl and JAK pathways. JAK kinases are critical for cytokine/growth factor signaling, and may be associated with human cancer.

#### Nonclinical safety issues relevant to clinical use

The toxicities in the target organs identified in the animals, i.e., hematopoietic (anemia) and lymphoid (infections), hepatobiliary (increased liver enzymes), renal, and cardiovascular (cardiac failure, angina pectoris) systems, and other organs such as GI tract (diarrhea, abdominal pain), lung (pleural effusion), eye (hemorrhage), thyroid (hyper- or hypothyroidism) and pancreas (increased lipase and amylase), were also reported in the patients as indicated in the parentheses. Despite the observations that nilotinib increased white blood cell or platelet counts in some species, inflammation and hemorrhage were seen in multiple organs in all species of animals tested. In light of the potential intervention of the Bcr-Abl and JAK, nilotinib can potentially compromise the host cytokine signaling and hence immune system.

Nilotinib exhibited pro-arrhythmic potential in the in vitro studies, despite no QT prolongation or other electrographical findings. Increased heart weights (over 10% from the control) observed in rats, dogs and monkeys may indicate potential cardiomyopathy in humans, despite minimal histopathological findings in animals. Rats treated with imatinib (Gleevec) for 6 months were found with no obvious histopathological lesions in the heart, except for increased heart weights. However, prolonged treatment of imatinib for 2 years led to cardiomyopathy in rats, a finding also reported in the patients (Kerkela et al., Nature Medicine 2006, 12:908-916). Nilotinib demonstrated dose-dependent embryofetal toxicities in rats and rabbits.

Hyperbilirubinemia observed in patients may be related to the finding that AMN107 induced inhibition of UGT1A1 mediated glucuronidation of bilirubin in pooled human liver microsomes.

## **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **4.1 Sources of Clinical Data**

The source of the clinical data was the Phase 1/2 trial conducted by the applicant. The submission includes data on treatment of CML-CP and CML-AP in patients intolerant of or resistant to imatinib. The primary population submitted in the initial NDA submission and the additional population data submitted in the 120-day efficacy and safety update were reviewed. All CML-CP patients had at least a 6-month follow-up and all CML-AP patients had at least a 4-month follow-up.

The phase 1 component of the study was designed to establish the MTD, define DLTs, and guide dosing in the phase 2 component.

External consultants were consulted during the course of the review.

#### 4.2 Tables of Clinical Studies

Only one study was relevant to the efficacy data in the submission as summarized in the table below. The single uncontrolled Phase 1/2 study had several cohorts and subsets of patients which were the basis for the indications. The Phase 2 components are still ongoing. Interim reports were submitted for the proposed indication. These were relevant to safety also. Safety data was also submitted for Studies 1101, 2103, 2109, 2101E3, E4, E5, E6, E7, E8, E9. The safety population in the CML-CP and CML-AP cohorts also included all patients enrolled who had received at least one dose of the drug.

**Table 1 Tables of Clinical Studies (Reviewer's Table)**

Study No.	Phase Study design	Population	No. of patients Enrolled	Treatment Regimen	Evaluations
2101	Phase 1A Dose-escalation study	Adult imatinib resistant/intolerant CML in CP, AP or BC; relapsed/refractory Ph+ ALL; other hematological malignancies	119 Age: 15-83 (56.2) M/F: 57/62	All qd: 69 400 mg bid: 32 600 mg bid: 18	MTD, DLT
2101 E2	Phase 2, arm 4, group A	Imatinib resistant/intolerant CML-CP	132 Age: 26-85 (58) M/F: 72/60	400 mg bid 600 mg bid	Efficacy (MCyR, CHR), safety
2101 E1	Phase 2, arm 3, group A	Imatinib resistant/intolerant CML-AP	64 Age: 24-79 (61) M/F: 34/30	400 mg bid 600 mg bid	Efficacy (MCyR, HR), safety

MTD=maximum tolerated dose

DLT=dose limiting toxicity

MCyR=Major cytological response

CHR=Complete hematological response

HR= hematological response

### **120-Day Efficacy and Safety Update**

The 120-day efficacy and safety update provided further efficacy data with longer follow-up for the 132 CML-CP and the 64 CML-AP patients included in the primary population submitted in the initial NDA and also included an additional 148 CML-CP and 41 CML-AP patients. The updated patient enrollment is shown in the table below. Supportive data were from CML-CP and CML-AP patients with prior tyrosine kinase inhibitor (TKIs) therapy in addition to imatinib.

**Table 2 12-Day Efficacy Update Enrollment (Reviewer's Table)**

Study No.	Phase	Population	Primary Enrollment	Additional Enrollment
2101 E2	Phase 2, arm 4, group A	Imatinib resistant/intolerant CML-CP	132 10 months follow-up	148 6 months follow-up
2101 E1	Phase 2, arm 3, group A	Imatinib resistant/intolerant CML-AP	64 8 months follow-up	41 4 months follow-up
2101 E8	Phase 2, arm 4, Group B	Imatinib/other TKI resistant/intolerant CML-CP	26	22
2101 E7	Phase 2, arm 3, Group B	Imatinib/other TKI resistant/intolerant CML-AP	10	11

Source: Table 1-1, SCE, 120-day Update

The applicant also stated that new data led to changes in previous tyrosine kinase inhibitor (TKI) history for 13 patients ( 1 CML-AP and 12 CML-CP).

Safety data was submitted for 318 CML-CP patients and 120 CML-AP patients.

*Reviewer's Comments:*

*The 120-day efficacy and safety update submitted on 26 Jan 2007 did not include any datasets for review. The applicant subsequently submitted the datasets on 13 March 2007 when requested by the FDA. Due to the large number of patients in the additional enrollment populations, it was decided to review all the efficacy and safety data.*

### **4.3 Review Strategy**

The review included:



Houston, TX 77030			
00301	2101 E2	5	2
Oliver G Ottman	2101 E1	5	3
Johann Wolfgang Goethe Universitat Zentrum der Inneren Medizin 60690 Frankfurt			

On May 16, 2007, the Agency received a communication from Novartis regarding a pending lawsuit against them. The complaint appeared to be that improper statistical data were reported to the FDA due to improper recording and reporting of data, failure to follow proper statistical protocols and use of an obsolete, safety reporting system called Standard Tables and Listing (STL), which may not be a validated system accepted by the Agency and may provide inaccurate data. Also, inaccurate dates may have been used to compress duration of adverse events. There are also charges that there were changes to the analyses plans without informing the Agency resulting in a fraudulent attempt to exaggerate the Summary of Clinical Efficacy and Safety. Based on the initial complaint, the Division of Scientific Investigations initiated a “for-cause” audit on the Company site.

*Reviewer’s Comment:*

*There were no prejudices identified by the FDA inspection team. The reader is referred to the review by Robert Young, MD, for complete details.*

**4.5 Compliance with Good Clinical Practices**

The informed consents met Federal and International standards. The protocol violations are described in the section summarizing efficacy. The trials appear to have been conducted in accordance with acceptable ethical standards.

The sponsor submitted a certification that debarred persons were not used in the conduct of the trials connected with this application, signed June 12, 2006.

**4.6 Financial Disclosures**

The applicant collected Financial Disclosures from all the principle investigators and sub-investigators. FDA Certification Form 3454 was signed by Dr. Aaron Weitzman, Clinical Program Leader, Novartis Pharmaceuticals Corporation. Disclosable financial arrangements and interests were submitted as follows for 5 investigators.

**Table 4 Financial Arrangements (Applicant's Table)**

Investigator	Study No.	Center No.	Amount Disclosed	Category of Disclosure
			> \$25,000	Honorarium
			> \$25,000	Honorarium
			> \$25,000	Honorarium
			> \$25,000	Honorarium
			> \$25,000	Honorarium

Source: finaninfo.pdf

## 5 CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

This section is excerpted from the Clinical Pharmacology Review by Qi Li, PhD. The reader is referred to the Clinical Pharmacology reviews for more detail.

Nilotinib is absorbed following oral administration. The bioavailability of nilotinib was increased when given with a meal. The median time to reach  $C_{max}$  of nilotinib was 3 hours. Drug elimination half-lives averaged about 17 hours. The increase in nilotinib AUC was generally dose-proportional over the dose range of 50 mg to 400 mg, but AUC appeared to plateau at dose levels starting at 400 mg.

As administered in Phase 2 and to minimize the effect of food on nilotinib bioavailability, nilotinib should be taken at least 2 hours after food intake, and food intake should be avoided for 1 hour after drug administration.

Age, body weight, or ethnic origin were not found to significantly affect the pharmacokinetics of nilotinib, whereas there is an effect of gender, with exposure to nilotinib in female patients being approximately 12% greater than in male patients.

The extent of nilotinib binding to human plasma protein is high (98% on average), and independent of concentration. The major metabolic pathway of nilotinib in humans involved hydroxylation of the methyl group in the methyl imidazole ring with further oxidation of the hydroxyl group to a carboxylic acid. CYP3A4 is expected to be the main contributor to the oxidative metabolism of nilotinib in humans with CYP2C8 making a minor contribution. Unchanged nilotinib represented 88% of the total drug-related serum exposure. In healthy subjects, co-administration of nilotinib with ketoconazole, a strong inhibitor of CYP3A4, increased nilotinib  $C_{max}$  by 84% and AUC by 3-fold on average. In healthy subjects, co-administration of rifampin with nilotinib decreased  $C_{max}$  and AUC of nilotinib by 64% and by 80% on average, respectively. Concurrent treatment with strong CYP3A4 inhibitors and inducers

should be avoided if possible; otherwise, dose adjustment of nilotinib will be needed.

Nilotinib is a potent inhibitor of CYP2C8, CYP2C9, CYP3A4/5 and UGT1A1, and a moderately potent inhibitor of CYP2C19 and CYP2D6. When a single oral 600 mg dose of nilotinib was co-administered with a 4 mg dose of midazolam (CYP3A4 substrate) in healthy subjects, nilotinib was found to increase the midazolam exposure by 30%. In vitro studies suggest that nilotinib may induce CYP2B6, CYP2C8, CYP2C9, CYP1A1, CYP1A2 and CYP3A4. Nilotinib was found to be a substrate and an inhibitor for P-gp mediated efflux.

Altered renal function is not likely to affect nilotinib pharmacokinetics, as no unchanged drug or metabolites were found in the urine.

No formal study has been conducted in children. No formal study has been conducted in patients with hepatic impairment. Excretion of nilotinib occurred exclusively through the fecal route.

## 5.2 Pharmacodynamics

Nilotinib prolongs the QT interval. In a healthy volunteer cardiac safety study, administration of nilotinib was associated with concentration-dependent QT prolongation. At exposures that were 26% lower than the therapeutic exposures observed in patients, the maximum mean placebo-adjusted QTcF change from baseline was 18 msec (1-sided 95% Upper CI: 26 msec).

A pharmacogenetic analysis examining the polymorphism of UGT1A1 and its potential association with hyperbilirubinemia during nilotinib treatment was conducted. In this study, The (TA)<sub>7</sub>/(TA)<sub>7</sub> genotype was associated with a statistically significant increase in risk of hyperbilirubinemia relative to the (TA)<sub>6</sub>/(TA)<sub>6</sub> and (TA)<sub>6</sub>/(TA)<sub>7</sub> genotypes.

Twice-daily dosing increases bioavailability with the 400 mg b.i.d. clinical dose providing 35% greater bioavailability than 800 mg q.d. Dose adjustment in patients with renal impairment is not considered necessary. Dose adjustment on the basis of age, body weight, or sex, is not considered necessary. Caution should be exercised when using nilotinib in patients with hepatic impairment. Concurrent treatment with strong CYP3A4 inhibitors should be avoided. Caution should be exercised when co-administering nilotinib with CYP3A4 substrates having a narrow therapeutic index.

## 5.3 Exposure-Response Relationships

There is an exposure-response relationship for the effectiveness of nilotinib. Higher nilotinib dose and systemic exposure were associated with increased efficacy response rates (hematologic response for CML-AP patients and cytogenetic response for CP patients).

Various adverse events (AE) and lab abnormalities were found to be nilotinib exposure-dependent. Nilotinib prolongs QT interval. In a healthy volunteer study designed to assess the

effects of Tasisna on the QT interval, administration of Tasisna was associated with concentration-dependent QT prolongation. At exposures that were 26% lower than the therapeutic exposures observed in patients, the maximum mean placebo-adjusted QTcF change from baseline was 18 msec (1-sided 95% Upper CI: 26 msec). There was evidence of increased total bilirubin, ALT, AST and lipase with nilotinib exposure. Caution is recommended in patients with hepatic impairment and patients with a history of pancreatitis.

## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

The proposed indication is:

Tasisna® (nilotinib) is indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to  prior therapy including imatinib

*Reviewer's Comment:*

*The indications for the two populations are similar to those for which dasatinib was given accelerated approval.*

#### 6.1.1 Methods

The results of all cohorts and subsets of the submitted Phase 1/2 trial were used in the efficacy review to support the proposed indication. The phase 1 dose-escalation (2101) contains efficacy information for both the chronic and accelerated phases CML. The CML chronic phase arm (CML-CP) in protocol 2101 (2101E2, arm 4, group A) and the CML accelerated phase (CML-AP) arm in protocol 2101 (2101E1, arm 3, group A) addresses each category of patients.

#### 6.1.2 General Discussion of Endpoints

Primary and secondary endpoints differed in the chronic phase arm and accelerated phase arm. The rationale for differences between early chronic phase CML (CML-CP) response criteria and advanced accelerated phase CML (CML-AP) response criteria is that cytogenetic responses are difficult to evaluate in advanced patients because of marrow fibrosis and poor marrow reserves.

In June 28, 2006, dasatinib (Sprycel) received accelerated approval for a similar indication based on the endpoints of major cytogenetic response and confirmed hematologic response with a relative follow-up of approximately 5.6 months in the CML-CP and CML-AP patients respectively.

The different endpoints are shown below.

**Table 5 Endpoints in CML-CP and CML-AP (Reviewer's Table)**

<b>Endpoints</b>	<b>CML CP</b>	<b>CML AP</b>
Primary endpoint	Major cytogenetic response (MCyR)	Overall confirmed hematologic response (HR)
Secondary endpoint	Time to MCyR Duration of MCyR Complete hematologic response (CHR) Time to CHR	Time to HR Duration of HR MCyR Time to MCyR Duration of MCyR

*Reviewer's Comments:*

*Confirmed cytogenetic responses and confirmed hematologic responses are acceptable surrogate endpoints and were used for the approval of dasatinib. These have been shown to predict clinical benefit in Ph + CML patients in the imatinib clinical development and were the basis of selection of these endpoints. To be a surrogate endpoint reasonably likely to predict clinical benefit, validated bone marrow cytogenetics is considered the test of choice. Although the protocol specified that FISH was used when bone marrow cytogenetics were inadequate, FISH is not a validated test.*

*Confirmed hematologic response and no evidence of leukemia in the advanced disease setting, CML-AP, is considered to be the primary endpoint reasonably likely to predict clinical benefit and therefore supportive of accelerated approval. These were used for the approval of dasatinib. Overall hematologic response which includes confirmed hematologic response, no evidence of leukemia and return to chronic phase is considered less clinically significant. Therefore, the reviewers do not recommend inclusion of return to chronic phase in the assessment of hematologic response for CML-AP patients.*

*There was no independent assessment of the endpoints in the protocol.*

*All endpoints were adjudicated by the reviewer. Consultations with external consultants were conducted during the review process.*

### 6.1.3 Study Design

Study 2101 is a currently ongoing Phase 1/2 open-label study. Patients in Phase II of Study 2101 were enrolled in the following disease categories:

- Arm 1: Relapsed/refractory Ph+ ALL
- Arm 2: Imatinib-resistant or -intolerant Ph+ CML in BC (Group A and Group B)
- Arm 3: Imatinib -resistant or -intolerant Ph+ CML in AP (Group A or Group B)
- Arm 4: Imatinib -resistant or -intolerant Ph+ CML in CP (Group A or Group B)
- Arm 5: Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia (HES/CEL)

- Arm 6: Systemic Mastocytosis (SM)

CML patients in arms 2, 3 and 4 were divided into two separate groups. Group A had no prior treatment with other TKIs except imatinib; Group B included patients who had prior treatment with other investigational TKIs in addition to imatinib. Group A of Arms 3 and 4 represents the pivotal efficacy data for this submission.

Study 2101 was a multi-center study conducted in 41 centers in 10 participating countries at the United States and Europe.

Study 2101 was included in the NDA submission as three separate study reports:

- The Phase IA dose-finding component included 119 patients with imatinib-resistant CML in CP, AP, and BC and relapsed/refractory Ph+ acute lymphoblastic leukemia (ALL)
- The Phase II component intended for registration included
  - 132 patients imatinib-resistant/intolerant Ph+ CML in CP
  - 64 imatinib-resistant/intolerant Ph+ CML in AP

The dose selected for Phase 2 was 400 mg b.i.d.

### **Study 2101**

#### Objectives and Endpoints

##### Primary objectives

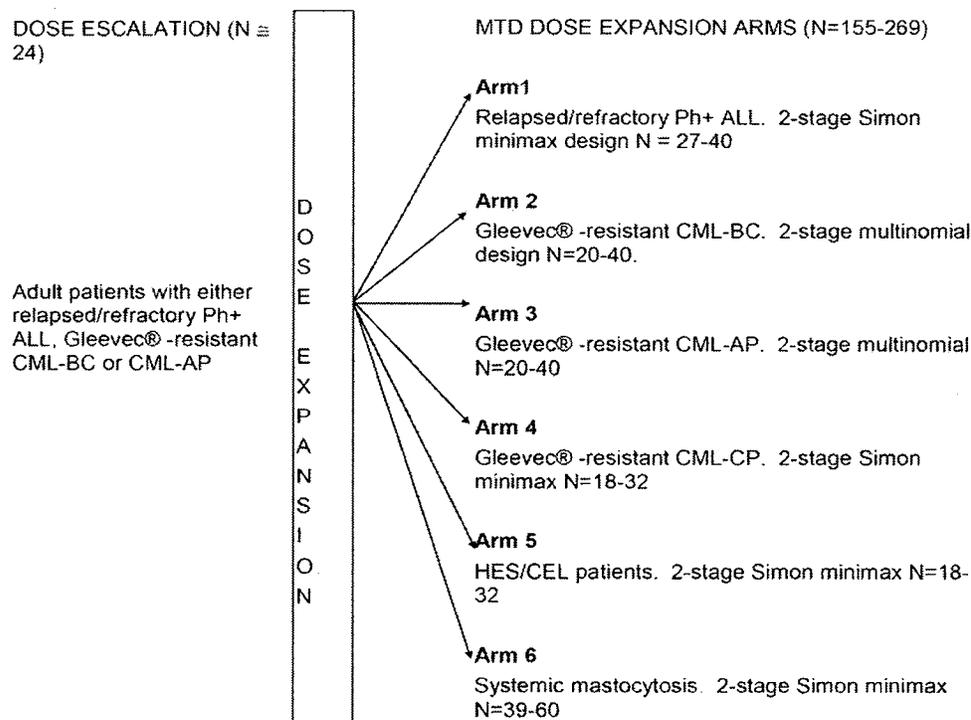
- To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of AMN107 as a single agent when administered as an oral once-daily dose to adult patients with Gleevec®-resistant CML in accelerated phase or blast crisis, or relapsed/refractory Ph+ ALL
- To characterize the pharmacokinetic profile of AMN107 in plasma and, where samples are available, in tumor cells and normal hematopoietic cells

##### Secondary objectives

- To characterize the safety and tolerability of AMN107, including acute and chronic toxicities, in patients with Gleevec®-resistant CML in accelerated phase or blast crisis, relapsed/refractory Ph+ ALL, and other hematologic malignancies
- To assess changes in the following parameters, pre and post therapy, in normal and malignant cells taken from the bone marrow and/or blood: Bcr-Abl phosphorylation status, Crk-L, C-Kit, PDGFR, STAT 5, AKT phosphorylation status, Q-RT-PCR to detect the presence of Bcr-Abl transcripts, and measures of proliferation and apoptosis
- To investigate tumor-specific mutations and gene expression changes in blood and bone marrow
- To investigate the effects of genetic variation in drug metabolism genes, hematologic malignancy genes and drug target genes on patient response for those patients who agree to participate

- At the MTD, to evaluate safety and preliminary anticancer activity according to 2-stage statistical designs in: relapsed/refractory patients with Ph+ ALL, Gleevec®-resistant CML blast crisis patients, Gleevec®-resistant CML accelerated phase patients, Gleevec®-resistant CML chronic phase patients, HES/CEL patients, and systemic mastocytosis patients. Patients who are Gleevec® intolerant (defined as patients who have discontinued Gleevec® therapy due to a grade 3 or 4 adverse event and have not had a major response to Gleevec®) will be assigned to the appropriate disease specific-treatment group

### Schematic Study design



A modified continuous reassessment method (MCRM) was used for dose-level selection and to determine MTD.

Eligibility (verbatim Section 3.3.2, original protocol, Mar 29, 2004)

#### Inclusion criteria

- Patients with a cytopathologically confirmed diagnosis of Ph+ ALL who are either relapsed after or refractory to standard therapy or patients with CML in blast crisis or accelerated phase who are resistant to Gleevec® Patients with Ph+ ALL who have minimal residual disease following stem cell transplantation may only be enrolled during the dose escalation portion of the study

- Following MTD determination, patients with a cytopathologically confirmed diagnosis of either CML in chronic phase who are Gleevec® resistant, systemic mastocytosis or hypereosinophilic syndrome/ chronic eosinophilic leukemia
- Patients with systemic mastocytosis or hypereosinophilia must have a clinical indication for treatment. HES/CEL patients should meet standard disease-definition criteria HES Systemic mastocytosis patient should meet standard disease-definition criteria
- Following MTD determination, patients with any of the eligible diseases who are Gleevec® intolerant (defined as patients who have discontinued Gleevec® therapy due to a grade 3 or 4 adverse event and have not had a major response to Gleevec®)
- Age  $\geq$  18 years old
- WHO Performance Status of  $\leq$  2
- Patients must have the following laboratory values:
  - White blood cell count (WBC)  $\leq$   $30 \times 10^9/L$ . Cytoreductive therapy with hydroxyurea, or vincristine, or cyclophosphamide is permitted; however, no treatment may be given in the 7 days prior to first administration of AMN107 except hydroxyurea and corticosteroids, which can be administered up to 48 hours prior to first administration of AMN107
  - Potassium  $\geq$  LLN (lower limit of normal) or correctable with supplements
  - Total calcium (corrected for serum albumin)  $\geq$  LLN or correctable with supplements
  - Magnesium  $\geq$  LLN or correctable with supplements
  - Phosphorus  $\geq$  LLN or correctable with supplements
  - ALT and AST  $\leq$  2.5 x ULN or  $\leq$  5.0 x ULN if considered due to tumor
  - Alkaline phosphatase  $\leq$  2.5 x ULN
  - Serum bilirubin  $\leq$  1.5 x ULN
  - Serum creatinine  $\leq$  1.5 x ULN or 24-hour creatinine clearance  $\leq$  50 ml/min
- Written informed consent

#### Exclusion criteria

- Cytopathologically confirmed CNS infiltration (in absence of suspicion of CNS involvement, lumbar puncture is not required)
- Impaired cardiac function, including any one of the following
  - LVEF  $<$  45% as determined by MUGA scan or echocardiogram
  - Complete left bundle branch block
  - Use of a cardiac pacemaker
  - ST depression of  $>$  1mm in 2 or more leads and/or T wave inversions in 2 or more contiguous leads
  - Congenital long QT syndrome
  - History of or presence of significant ventricular or atrial tachyarrhythmias
  - Clinically significant resting bradycardia ( $<$  50 beats per minute)
  - QTc  $>$  480 msec on screening ECG
  - Right bundle branch block plus left anterior hemiblock, bifascicular block
  - Myocardial infarction within 3 months prior to starting AMN107

- Angina pectoris
- Other clinically significant heart disease (e.g., congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of AMN107 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
- Use of therapeutic warfarin.
- Acute or chronic liver or renal disease considered unrelated to tumor
- Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol
- Treatment with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF)  $\leq$  1 week prior to starting study drug. Erythropoietin is allowed.
- Patients who are currently receiving treatment with any of the medications listed in post-text supplement 4 and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug. The medications listed in post-text supplement 4 have the potential to prolong the QT interval.
- Patients who have received chemotherapy  $\leq$  1 week (6 weeks for nitrosurea or mitomycin- C) or who are within 5 half-lives of their last dose chemotherapy dose prior to starting study drug or who have not recovered from side effects of such therapy. Exceptions are cytoreductive therapy as outlined in the Inclusion Criteria
- Patients who have received Gleevec®  $\leq$  1 week or who have not recovered from side effects of such therapy
- Patients who have received immunotherapy  $\leq$  1 week prior to starting study drug or who have not recovered from side effects of such therapy
- Patients who have received any investigational drug  $\leq$  4 weeks or investigational cytotoxic agent within 1 week (or who are within 5 half-lives of a previous investigational cytotoxic agent) prior to starting study drug or who have not recovered from side effects of such therapy
- Patients who have received wide field radiotherapy  $\leq$  4 weeks or limited field radiation for palliation  $<$  2 weeks prior to starting study drug or who have not recovered from side effects of such therapy
- Patients who have undergone major surgery  $\leq$  2 weeks prior to starting study drug or who have not recovered from side effects of such therapy
- Patients who are pregnant or breast feeding, or adults of reproductive potential not employing an effective method of birth control. (Women of childbearing potential must have a negative serum pregnancy test within 48 hrs prior to administration of AMN107). Post menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Male and female patients must agree to employ an effective barrier method of birth control throughout the study and for up to 3 months following discontinuation of study drug

- Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)
- Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention.
- Patients unwilling or unable to comply with the protocol

Schedule of Assessments

Examination	Base-line <sup>1</sup>	Cycle 1								Cycle 2						All subsequent cycles			Study Completion <sup>23</sup>
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
VISIT No. <sup>*</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		
Day of Cycle	14-1	1	2	3	8	15	16	22	28	1	8	15	22	28	1	15	28	Last	
Written Informed Consent	X																		
Inclusion/Exclusion Criteria	X																		
Demography, Relevant Medical History/Current Medical Conditions	X																		
Prior concomitant medications/Significant non-drug therapies <sup>2</sup>	X																		
Diagnosis and extent of tumor	X																		
Prior antineoplastic therapies	X																		
Height (baseline only), weight <sup>2</sup>	X	X								X					X			X	
Physical examination, vital signs <sup>3</sup>	X	X	X			X	X			X		X			X			X	
WHO Performance Status <sup>3</sup>	X	X								X					X			X	
Chest x-ray <sup>4</sup>	X																		
Hematology <sup>5</sup>	X	X			X	X		X		X	X	X	X		X	X		X	
Coagulation panel <sup>6</sup>	X									X								X	
Serum Chemistries <sup>7</sup>	X	X			X	X		X		X	X	X	X		X	X		X	
Urinalysis <sup>8</sup>	X																	X	
Serum Pregnancy test <sup>9</sup>	X																		
Concomitant Medications <sup>10</sup>	X	←←←←←←←←←←←←←←←← CONTINUOUS →→→→→→→→→→→→→→→→																	
Adverse Events		←←←←←←←←←←←←←←←← CONTINUOUS →→→→→→→→→→→→→→→→																	
AMN107 dosing		←←←←←←←←←←←←←←←← CONTINUOUS →→→→→→→→→→→→→→→→																	
Pharmacokinetic blood samples <sup>11</sup>		X	X		X	X	X	X	X						X				
12-lead ECG <sup>12</sup>	X	X		X	X	X		X	X					X				X	
Cardiac enzymes <sup>13</sup>		X	X	X		X			X					X				X	

Examination	Base-line <sup>1</sup>	Cycle 1								Cycle 2						All subsequent cycles			Study Completion <sup>23</sup>
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
VISIT No. <sup>*</sup>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		
Day of Cycle	14-1	1	2	3	8	15	16	22	28	1	8	15	22	28	1	15	28	Last	
Cardiac imaging (MUGA/ECHO) <sup>14</sup>	X																	X	
Radiologic assessment of tumor (if required) <sup>15</sup>	X								X					X				(X)	
Radiologic assessment of bone in SM patients <sup>16</sup>	X							(X)						(X)				(X)	
Bone marrow aspirate and/or biopsy for diagnosis and biomarkers <sup>16</sup>	X					X		X						X				(X)	
Cytogenetics <sup>17</sup>	X							(X)						(X)				(X)	
Blood for pharmacodynamic biomarker analyses <sup>22</sup>		X	X			X	X		X					X				(X)	
Blood for exploratory biomarker analyses <sup>16 20</sup>		X				X			X					X				(X)	

Examination	Base-line <sup>1</sup>	Cycle 1								Cycle 2						All subsequent cycles			Study Completion <sup>23</sup>
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
VISIT No.*	1																		
Day of Cycle	14-1	1	2	3	8	15	16	22	28	1	8	15	22	28	1	15	28	Last	
Cardiac imaging (MUGA/ECHO) <sup>14</sup>	X																	X	
Radiologic assessment of tumor (if required) <sup>15</sup>	X								X					X			(X)	X	
Radiologic assessment of bone in SM patients <sup>19</sup>	X								(X)					(X)			(X)	(X)	
Bone marrow aspirate and/or biopsy for diagnosis and biomarkers <sup>16</sup>	X					X			X					X			(X)	X	
Cytogenetics <sup>17</sup>	X								(X)					(X)			(X)	(X)	
Blood for pharmacodynamic biomarker analyses <sup>22</sup>		X	X			X	X		X					X			(X)	X	
Blood for exploratory biomarker analyses <sup>19, 20</sup>		X				X			X					X			(X)	X	
Antineoplastic medication/therapies <sup>21</sup>	X																	X	

\* For Electronic Data Management (EDM) entry.  
<sup>1</sup> Baseline evaluations must be performed ≤ 14 days prior to cycle 1 administration of AMN107, unless otherwise stated.  
<sup>2</sup> Record all medications given ≤ 4 weeks prior to the administration of AMN107  
<sup>3</sup> Physical examination, vital signs (temperature, respiratory rate, blood pressure and pulse), height (baseline only), weight and assessment of WHO performance status must be performed at:  
baseline  
day 1 of each cycle prior to the administration of AMN107 or ≤ 72 hours prior to dosing  
intended day 1 of each cycle (if AMN107 is being withheld)  
physical examination and vital signs only must be performed on or within 24 hours of day 15 of cycles 1 and 2  
at the time of study completion  
On days of full PK assessment during cycle 1(days 1 and 15), vital signs must be performed at 0h (pre-dose), and blood pressure and pulse at 1h, 2h, 3h, 4h, 7h, 10h and 24h post dose. The 24h timepoint is prior to ingestion of AMN107 the following day.  
If the administration of AMN107 is interrupted due to unacceptable toxicities, see Section 3.4.1.6 for the required frequency of evaluations.  
<sup>4</sup> Chest x-ray must be performed at baseline and should be repeated if clinically indicated.  
<sup>5</sup> Hematology includes the following parameters: complete blood count (CBC) including a total white blood cell count (WBC), neutrophil count (including bands).

**Reviewer's Comments:**

According to the Study 2101 Phase 2 exclusion criteria, all patients with any evidence of impaired cardiac function were excluded from the study. These included LVEF < 45%, bundle branch blocks, cardiac pacemaker, ST depression of > 1mm in 2 or more leads and/or T wave inversions in 2 or more contiguous leads, congenital long QT syndrome, history of or presence of significant ventricular or atrial tachyarrhythmias, bradycardia (< 50 beats per minute), QTc > 480 msec on screening ECG (using the QTcF formula), myocardial infarction within 3 months prior and angina pectoris.

The use of concomitant administration of agents that prolong the QT interval and CYP 3A4 inhibitors while patients are receiving AMN107 were contraindicated but not an exclusion criteria. It was strongly recommended that in cases where administration of a QT prolonging agent or a CYP 3A4 inhibitor cannot be avoided, an ECG be obtained 24 to 48 hours and one week after initiating the concomitant therapy.

**Definition of Imatinib Resistance and Intolerance, Phase 2 (Verbatim, Protocol Amendment #4, Mar 26, 2005)**

**Imatinib resistance in CML-chronic phase (CML-CP)**

Imatinib resistance in CML-CP includes patients who meet objective criteria for persistent disease or disease progression during imatinib therapy as outlined in both 1 and 2:

1. Any of the following occurring during imatinib therapy
  - Patients who have failed to achieve CHR after 3 months of imatinib therapy or have lost a CHR
  - Loss of CHR defined as any of the following documented 2 times, at least 2 weeks apart:
    - i. WBC  $\geq 20.0 \times 10^9/L$  and not attributable to other causes (e.g. infection)
    - ii. Platelet count  $\geq 600 \times 10^9/L$
    - iii. Appearance of  $\geq 5\%$  myelocytes + metamyelocytes in the peripheral blood
    - iv. Appearance of blasts or promyelocytes in the peripheral blood
    - v. Splenomegaly to a size  $\geq 5$  cm below the left costal margin
  - Patients who have failed to achieve at least a minimal cytogenetic response after 6 months of imatinib therapy or patients who have lost a minimal cytogenetic response documented on 2 separate occasions
  - Patients who have failed to achieve a major cytogenetic response after 12 months of imatinib therapy or patients who have lost a major cytogenetic response documented on 2 separate occasions.
  - Cytogenetic relapse, defined by  $\geq 30\%$  increase in bone marrow Ph+ metaphase cells, documented on 2 separate occasions
  - Clonal evolution (patients with clonal evolution who do not meet any of the other criteria outlined in 1 are eligible for enrollment but are not evaluable in the primary efficacy analysis)
2. Patients otherwise eligible for study receiving  $<600$  mg per day must be treated with  $\geq 600$  mg per day for a minimum of 3 months, unless they meet the criteria outlined below for the definition of imatinib intolerance, or unless there is a disease progression defined as any of the following:
  - Doubling of any of the following: total peripheral WBC, basophils, blasts or platelets, documented on 2 separate occasions at least 1 week apart
  - Development of grade 3/4 disease-related symptoms (bone pain, fever, weight loss, anorexia)
  - The presence of one of the following amino acid mutations detected by direct sequencing:
    - L248, G250, Q252, Y253, E255, T315, F317, H396

### **Imatinib resistance in CML-accelerated phase (CML-AP)**

For CML-AP patients, imatinib resistance was defined as meeting criteria 1 or criteria 2 below:

1. Any of the following during imatinib therapy with at least 600 mg per day (unless they met the criteria for imatinib intolerance):
  - Disease progression from CP to AP, occurring during imatinib therapy
  - Disease progression defined as  $\geq 50\%$  increase in peripheral white blood cell count, blast count, basophils, or platelets during imatinib therapy for AP
  - Lack of hematologic response in the bone marrow following a minimum of 4 weeks of imatinib therapy for AP
2. Patients otherwise eligible for study receiving  $<600$  mg per day were eligible if the presence of one of the following amino acid mutations was detected by direct sequencing:
  - L248, G250, Q252, Y253, E255, T315, F317, H396

Note: CML-AP patients who had become resistant during chronic phase and met the definition of imatinib resistance in CML-chronic phase were eligible.

### **Imatinib Intolerance in CML-CP and CML-AP**

Patients were considered imatinib-intolerant (at any dose and/or duration) if they had not had a major cytogenetic response to imatinib and have discontinued imatinib therapy due to Grade 3 or 4 adverse events that persisted in spite of optimal supportive care measures, for example: skin rash, fluid retention, cardiopulmonary events, thrombocytopenia, liver function abnormalities, peripheral neuropathy and diarrhea. In addition, patients who had Grade 2 adverse events related to imatinib therapy, in spite of optimal supportive care measures, that persisted for  $\geq 1$  month or that recurred more than 3 times whether dose is reduced or discontinued, also qualified as imatinib-intolerant.

### **Response Criteria (Verbatim, Amendment #4, Mar 26, 2005)**

#### **Response criteria for CML-CP**

##### Complete hematologic response (CHR)

- White-cell count of less than  $10 \times 10^9/L$ , a platelet count of less than  $450 \times 10^9/L$
- The presence of less than 5 % myelocytes plus metamyelocytes
- The presence of less than 20 percent basophils
- The absence of blasts and promyelocytes in peripheral blood, and the absence of extramedullary involvement

##### Cytogenetic response (within CHR)

Based on the prevalence of Ph+ metaphases among at least 20 metaphase cells in each bone marrow sample analyzed by standard metaphase cytogenetics

- Complete (0% Ph+ cells)
- Partial (1%-35% Ph+ cells)

- Minor (36%-65% Ph+ cells)
- Minimal (66%-95% Ph+ cells)
- None (>95% Ph+ cells)

Major cytogenetic responses are either complete or partial responses. In cases where the standard metaphase cytogenetics is inadequate (i.e., there are less than 20 metaphase cells), D-FISH will be used for assessment of cytogenetic response.

All patients who have a complete hematologic response must have a bone marrow assessment for cytogenetic response. In addition, cytogenetic response assessments must be performed at the end of cycles 3, 6, 9, and 12, and every 3 cycles thereafter.

Stable disease (SD)

- Failure to meet criteria for response and failure to meet criteria for disease progression.

Progression of disease (PD) (must fulfill any one of the following):

1. The development of accelerated-phase CML or blast-crisis CML (defined below)
  - CML in blast crisis: 30% blasts in peripheral blood or marrow or the presence of extramedullary disease (other than liver or spleen enlargement)
  - CML in accelerated phase (any one of the following):
    - >15% but <30% blasts in blood or bone marrow
    - $\geq 30\%$  blasts plus promyelocytes in peripheral blood or bone marrow (providing that <30% blasts present in bone marrow)
    - peripheral basophils  $\geq 20\%$
    - thrombocytopenia  $< 100 \times 10^9 /L$  unrelated to therapy
2. Loss of CHR (defined by the appearance of any of the following in two blood samples obtained at least two weeks apart):
  - A white-cell count of more than  $20 \times 10^9 /L$
  - A platelet count of at least  $600 \times 10^9 /L$
  - The appearance of extramedullary disease
  - The appearance of at least 5 percent myelocytes and metamyelocytes in the peripheral blood
  - The appearance of blasts or promyelocytes in the peripheral blood
3. Loss of major cytogenetic response as defined by
  - An increase in Ph-positive cells in metaphase by at least 30 percentage points on two cytogenetic analyses performed on two separate occasions
4. An increasing white-cell count defined as
  - a doubling of the count to more than  $20 \times 10^9 /L$  on two occasions at least one week apart in a patient who had never strictly had a complete hematologic response despite receiving maximally tolerated doses of therapy.

## Response criteria for CML-AP

Hematologic response (defined as complete hematologic response, marrow response/no evidence of leukemia, or return to chronic phase) lasting at least 4 weeks (i.e. confirmed response) assessed as:

### Complete hematological response (CHR)

- Myeloblast count less than 5% in bone marrow
- no myeloblasts in peripheral blood
- neutrophil count at least  $1.5 \times 10^9/L$
- Platelet count at least  $100 \times 10^9/L$
- No evidence of extramedullary involvement

### Marrow response (MR)/no evidence of leukemia (NEL):

- Myeloblast count less than 5% in bone marrow
- no myeloblasts in peripheral blood
- neutrophil count at least  $1.0 \times 10^9/L$
- Platelet count at least  $20 \times 10^9/L$  (without platelet transfusion or evidence of bleeding)
- No evidence of extramedullary involvement

### Return of chronic phase (RTC)

- Less than 15% myeloblasts in peripheral blood and bone marrow
- Less than 30% myeloblasts plus promyelocytes in peripheral blood and bone marrow
- Less than 20% peripheral basophils
- No other peripheral involvement other than liver or spleen

<b>Chronic phase</b> Imatinib-resistant/intolerant
Imatinib resistant or intolerant Philadelphia chromosome-positive CML in chronic phase is defined by the presence of all of the following criteria: 1. < 15% blasts in PB and BM 2. < 30% blasts + promyelocytes in PB and BM 3. < 20% basophils in PB 4. $\geq 100 \times 10^9/L$ platelets (for imatinib-intolerant patients, a platelet count of $< 100 \times 10^9/L$ is not considered as a violation of this condition) 5. No extramedullary involvement other than liver or spleen
<b>Cytogenetic response (CyR):</b> <ul style="list-style-type: none"><li>• <b>Complete:</b> 0% Ph+ cells</li><li>• <b>Partial:</b> 1% - 35% Ph+ cells</li><li>• <b>Minor:</b> 36% - 65% Ph+ cells</li><li>• <b>Minimal:</b> 66% - 95% Ph+ cells</li><li>• <b>None:</b> &gt; 95% Ph+ cells</li></ul>

### **Cytogenetic response (within CHR or marrow response)**

Based on the prevalence of Ph+ metaphases among at least 20 metaphase cells in each bone marrow sample analyzed by standard metaphase cytogenetics.

- Complete (0% Ph+ cells)
- Partial (1%-35% Ph+ cells)
- Minor (36%-65% Ph+ cells)
- Minimal (66%-95% Ph+ cells)
- None (>95% Ph+ cells)

Major cytogenetic responses are either complete or partial responses. In cases where the standard metaphase cytogenetics is inadequate (i.e., there are less than 20 metaphase cells), D-FISH will be used for assessment of cytogenetic response. All patients who have a complete hematologic or marrow response must have a bone marrow assessment for cytogenetic response.

#### **Stable disease (SD)**

- Failure to meet criteria for response and failure to meet criteria for disease progression.

#### **Progressive disease (PD)**

The development of blast crisis, as defined by

- CML in blast crisis: 30% blasts in peripheral blood or marrow or the presence of extramedullary disease (other than liver or spleen enlargement). Or
- Recurrence of CML-AP in a patient who had a hematological response as defined as:
  - >15% but <30% blasts in blood or bone marrow
  - ≥ 30% blasts plus promyelocytes in peripheral blood or bone marrow (providing that <30% blasts present in bone marrow)
  - peripheral basophils ≥ 20%
  - thrombocytopenia <100 X 10<sup>9</sup>/L unrelated to therapy

### **Interim analyses**

The protocol-specified Group A efficacy analysis for CML-CP is defined as the time that the first 132 patients either completed 24 weeks of treatment, discontinued the study, or a confirmed hematologic response had been observed.

The claim of efficacy for CML-AP patients was based on the first 64 patients included in this report who completed 4 months of treatment or discontinued study. The results of the efficacy analysis on the 132 patients with 24 weeks (6 months) of treatment will be provided at a later time.

### **Protocol amendments**

Ten amendments were made to the original protocol (dated Mar 29, 2004). Amendment 1 through 3 were for Phase I only. The key features of each amendment are given below:

#### Amendment No. 1 (Sept 9, 2004)

The following changes were made to the original protocol: • Inclusion of language and guidelines for intra-patient dose escalation to achieve adequate disease control • Inclusion of guidelines for safety assessment during intra-patient dose escalation • Modification/clarification of timing of evaluations at study completion • Allow longer duration of hydroxyurea usage, as it may be necessary to control high white blood cell counts • Update and clarify visit schedule time points to adequately assess safety following inpatient dose escalation • Update and clarify sample collection times for pharmacodynamic assessments • Administrative changes including inconsistencies with abbreviations were corrected in the document and additional background references were added.

#### Amendment No. 2 (Oct 1, 2004)

The purpose of this amendment was to allow patients with Gleevec resistant CML chronic phase (CML-CP) to be enrolled into the dose escalation component of the protocol (this population of patients was already included in the dose expansion component). This decision was based on the observation of acceptable safety and tolerability, as well as encouraging clinical activity among the first 34 patients enrolled in the initial four dose cohorts of this trial.

#### Amendment No. 3 (Nov 23, 2004)

The purpose of this amendment was to explore whether a every 12 hour dosing schedule (vs. the ongoing q.d. dosing schedule) would increase nilotinib plasma exposure. The pharmacokinetics had been dose proportional at dose levels ranging from 50 mg to 400 mg po q.d., but there was little change in exposure from 400 mg to 800 mg po q.d. Therefore, a more frequent dosing schedule was explored to determine whether exposure can be increased. The 800 mg once daily dose was well tolerated and did not define the DLT dose level for schedule 1. In addition, the PK profile of nilotinib suggested that twice daily dosing may increase the daily exposure of nilotinib. The dose schedule providing the highest exposure with a well tolerated safety profile will be the MTD dose schedule.

#### Amendment No. 4 (Mar 17, 2005)

The main purpose of this amendment was to modify the Phase II study design for patients with imatinib resistant and intolerant CML-BC, imatinib resistant and intolerant CML-AP, and imatinib resistant and intolerant CML-CP, in order to determine more definitively whether

nilotinib demonstrated clinical benefit in these groups of patients. In addition, inclusion criteria and concomitant medication were updated. Details are below:

- The study design for Phase II was changed in arm 2 (imatinib -resistant CML-BC patients), arm 3 (imatinib -resistant CML-AP patients) and arm 4 (imatinib -resistant CML-CP patients) to a Fleming single-stage design, and the number of patients per arm was increased from 40 to 132.
- Inclusion criteria for Phase II were modified to clarify diagnostic criteria for imatinib resistant and intolerant CML-BC, CML-AP, and CML-CP, HES/CEL and SM. Disease specific response criteria were modified and/or clarified for each arm, and efficacy evaluation times were specified for each arm. Definitions of imatinib resistance in CML-CP, AP and BC were expanded and definition of imatinib intolerance was added. Secondary efficacy endpoints for Phase II were added.
- The initial dose of nilotinib for Phase II was set at 400 mg bid, based on the safety and pharmacokinetic (PK) profile at this dose level determined in the Phase IA component of the trial.
- The phase II study was amended to require laboratory fractionation of bilirubin, and to allow the dose of nilotinib to continue without dose modification, at the discretion of the investigator, for isolated elevations of indirect bilirubin when there was no elevation in direct bilirubin or transaminases, and no evidence of hemolysis.
- Monitoring of serum lipase and amylase throughout the study, weekly during the first 28 days of therapy, and monthly thereafter, and dose modifications for pancreatitis and/or elevations in lipase were included.
- Response criteria for Ph+ ALL, CML (BC, AP and CP), SM and HES/CEL were revised to clarify and give additional detail as to how response is assessed and to specify the required duration of response.
- PK assessments were updated for Phase II to support population PK assessments in all 6 arms. In addition, cerebrospinal fluid will be taken in patients with Ph+ ALL who have a lumbar puncture anytime during the study to determine level of nilotinib. In Phase II, ECG and cardiac enzyme assessment schedules were modified to coincide with the Tmax on Day 1 and Day 8 (steady-state) of cycle 1, and with the updated schedule of PK assessments on Day 8. These assessments also continued at a frequency of once per cycle throughout the study.
- The sampling and analysis for exploratory biomarkers in Phase II was reduced. However, measurement of bcr-abl transcript levels and mutation status remained.

- Text in the protocol was revised to refer specifically to the Phase IA vs. Phase II component of the study. Where appropriate, subheadings were created for this purpose. In addition, references to ‘following MTD determination’ or ‘dose expansion phase’ have been changed to ‘in Phase II’.

Amendment No. 5 (Jul 21, 2005)

The main purposes of this amendment were (1) to include patients with prior investigational tyrosine kinase inhibitors (TKI) other than imatinib in order to clearly estimate the treatment effect of nilotinib in these subsets of patients; (2) to allow dose escalation to 600mg b.i.d. for patients who have not adequately responded; (3) to change time to progression (TTP) to time to treatment failure (TTF) to ensure that patients who discontinued for reasons other than progression were captured as a secondary efficacy variable, (4) to add an abdominal sonogram to baseline screening prior to initiating nilotinib therapy to explore whether the risk of hyperbilirubinemia and/or pancreatitis might be increased in patients with preexisting gall bladder pathology, including cholelithiasis, and (5) to modify the dose modification guidelines to include a de-escalation schedule at the 600 mg b.i.d. dose level (and revise for cardiac and hepatobiliary toxicities).

- Phase I patients who were on study when Amendment 5 was approved by the local ethics committees were to follow the same schedule, procedures (including blood collection for biomarkers) and dose administration as the Phase II patients to provide consistency across the study.
- Patients with Ph+ALL, and CML, with no prior dose modifications due to toxicity and in the absence of severe adverse drug reactions and severe non-leukemia related hematologic toxicities, may (at the investigators’ discretion) have had a dose increase to 600 mg b.i.d..
- All patients who discontinued from the study treatment were to have the study completion evaluations performed within 7 days prior to the day of study treatment completion.
- Since imatinib is cleared from circulation by 5 days, the wash-out period for imatinib was adjusted from 1 week to 5 days.
- To delineate population pharmacokinetics at 600mg b.i.d. dose level, additional blood samples were obtained on day 8 (allowing a window up to day 28). ECG monitoring was performed at the same time points to coincide with PK sampling following dose escalation.

Amendment No. 6 (Nov 9, 2005)

- Over enrollment on the CML arms, based on an urgent need priority, was permitted to allow patients access to nilotinib until initiation of the early access protocol (Study CAMN107A2109). The “urgent need” patient population was not included in the primary efficacy analysis, and their responses were summarized separately.

- Temporary lowering the dose for patients with systemic mastocytosis to reduce the risk of additional toxicities (possibly attributed to mast cell degranulation), with subsequent re escalation of the dose, was permitted upon resolution of these symptoms to = grade 1, and provided these toxicities did not recur.
- An additional dose modification decrease to 200 mg q.d. was added, as the Phase I data had shown clinical and biological activity at that dose level. Dose modification for QTcF = 500 ms was clarified.
- Biomarker analysis (FIP1L1-PDGFR $\alpha$  and c-KIT) for HES/CEL and SM arms was changed from optional to mandatory, to allow analysis for these putative biomarkers.
- The number of patients in which protein assay was performed was changed from 50 to all patients with CML (in Germany and Australia), provided that they signed the separate informed consent.
- The definition of cytogenetic response was clarified, removing \_\_\_\_\_ since cytogenetic response need not be within these parameters.
- Clarification was made to the definition of imatinib resistance in CML-AP and CML-BC to ensure that patients who became resistant in the chronic phase but were in BC or AP were included in the study.
- Collection procedures for blood and bone marrow sampling handling were made due to a change from the manufacturer of the \_\_\_\_\_
- The table of substrates of cytochrome P450 isoenzymes was changed to reflect results from a more detailed in vitro study (DDI2) with accurate Ki values. The DDI2 study results indicated that nilotinib may inhibit CYP2C9, 2C8, 3A4, and 2D6 in a clinical concentration range, as Ki values for those isoenzymes is lower than nilotinib concentrations observed at 400 mg bid in patients.

Amendment No. 7 (Jan 6, 2006)

The purpose of this amendment was to extend the date of enrollment for patients with an urgent need to receive treatment with nilotinib from 31-Dec-2005 to 31-Mar-2006, prior to initiation of Protocol CAMN107A2109 (the early access protocol). In addition:

- Patients who had been on study for a minimum of 3 cycles were be permitted to have visits performed by the local physician, provided they were not response or confirmation of response visits. The local physician was to conduct all protocol-required safety assessments, and the results were to be communicated to the Investigator.

- If the bone marrow aspirate was sufficient for analysis, bone marrow biopsy was not required.
- The definition of imatinib intolerance was revised to ensure that all categories of intolerance related to imatinib therapy was included.

Amendment No. 8 (Feb 10, 2006)

This safety amendment was a result of six reports of sudden death in patients on nilotinib, which were reported to health authorities globally through the expedited safety reporting process, and Investigator Notification letters.

The relationship of 4 these events to nilotinib was not certain (2 deaths were not related to nilotinib). The relatively early occurrence of 3 of these events suggested the possibility that ventricular repolarization abnormalities may have contributed to their occurrence.

Changes to the protocol (Phase I and Phase II) included:

- Contraindication, unless absolutely necessary, of concomitant administration of agents that prolonged the QT interval and CYP3A4 inhibitors. In cases where unavoidable, a strong recommendation that ECG be obtained 24 to 48 hours and one week after initiating the concomitant therapy.
- Revision of criteria for discontinuation or dose reduction of nilotinib based on ECG QTc prolongation: Patients with QTcF = 500 msec discontinue nilotinib immediately and not restart therapy unless a clear precipitant is identified, and the QTc returns to within 20 msec of baseline within two weeks. Patients with QTcF > 480 msec and =500 msec must have a follow-up ECG performed. If that ECG confirmed QTcF > 480 msec, dose of nilotinib reduced by half.

Changes to the protocol (Phase II only):

- Lowering of the maximal QTcF for inclusion: from 480 to 450 msec.
- Extension of timeframe for exclusion of patients who had sustained a myocardial infarction from 3 to 12 months.
- Exclusion of patients diagnosed with or treated for unstable angina during the past 12 months.
- Serum potassium and serum magnesium levels corrected to within normal limits prior to the first dose of study medication. Investigators were to monitor these levels as specified in the protocol (at least twice monthly) and to maintain serum potassium and serum magnesium levels with normal limits during the study.



anticipated (20%). The efficacy analysis was therefore performed when the first 64 patients either completed 4 months of treatment or discontinued study. Additional data on duration of effect would be provided along with safety data in the 120-day safety update.

### **Deviations from protocol-specified criteria by the applicant**

- To be included on the study CML-AP patients should never have been in CML-BC prior starting treatment. However, these patients were included if they satisfied all other the CML-AP criteria at baseline as their prognosis was considered worse than that of an AP patient who have never previously been in BC prior. This was allowed as it skewed the patient population towards being more, rather than less refractory.
- Thrombocytopenia  $<100 \times 10^9/L$  unrelated to therapy, as a criteria for recurrence CML-AP in patients with hematologic response, was not considered, as it was not possible to accurately link any platelet count of  $< 100 \times 10^9/L$  with an adverse event of thrombocytopenia that was unrelated to therapy.
- Patients must have had baseline evaluations performed within 14 days prior to first dose of nilotinib. However, extramedullary disease and bone marrow (positive for Philadelphia positive chromosome) were allowed if performed more than 14 days but within 28 days prior to first dose of nilotinib.

### **Biomarker**

Data analysis for the phosphorylation status of the biomarker CRK-L is ongoing, and results were not included in this CSR.

The applicant's initial plan was to submit registration dossier for CML AP and BC patients first followed by CML CP as an sNDA. However, the CML-BC patient cohort is now excluded from the initial submission, while results obtained in the CML-CP cohort are included. This is due to the slower than expected enrollment of the CML-BC cohort.

The time points for the primary analysis for test of efficacy in the Phase 2 portion of the study were changed to 6 months, instead of the previously planned 12 months (for CML-CP cohort) and to 4 months instead of 6 months (for CML-AP cohort). The rationale for this modification was based on the earlier time to response (than anticipated) in a significant number of patients enrolled in the Phase 1 portion of the study. The Phase 1A results demonstrated that the median time to best hematologic response for CML-AP patients was 84 days, with a 76% rate of hematologic response and the median time to best MCyR for CML-CP patients with and without baseline CHR were 56 and 112 days, respectively. On the basis of these observations, the sample size for CML-AP was reduced from 132 to 64 patients, and utilizing a revised 'response rate' assumption of 25% instead of 20%.

*Reviewer's Comments:*

- 1. The study design is a non-randomized, non-blinded, single study. The two cohorts, CML-CP and CML-AP, were two arms of a single protocol. At the time the development plan for nilotinib was designed, the Agency had agreed that a comparison to Interferon based on a literature review would be reasonable in the absence of a controlled trial in the CML-CP cohort. At that time, single-arm studies were considered appropriate for accelerated approval. Cytogenetic response and hematologic response were considered as surrogate efficacy endpoints.*
- 2. The Agency recommended the initially planned follow-up of 12 months for the CML-CP cohort and 6 months for the CML-AP cohort. The applicant chose the much shorter follow-up periods of 6 and 4 months respectively for each cohort.*
- 3. Phase 2 dose finding using the modified continuous reassessment method identified 600 mg bid as the dose. However, 400 mg bid was subsequently used as the phase 2 dose due to toxicities seen at the higher dose. Patients were allowed to dose escalate to 600 mg bid in the protocol.*
- 4. The CML-CP patient population was added to the protocol in Amendment #4, dated Mar 17, 2005.*
- 5. Sample size calculations for the CML-AP cohort were changed while the study was ongoing based on a revised response rate and reduced from 132 to 64 patients. The Agency cautioned against reducing the sample size.*
- 6. The final definitions of imatinib resistance and intolerance for CML-CP and CML-AP patients were in Amendment #7, dated Jan 6, 2006.*
- 7. The statistical analysis plan was after date of cutoff with the last amendment performed two weeks prior to NDA submission.*
- 8. Safety was well addressed in the protocol.*
- 9. This protocol was not submitted under a Special Protocol Assessment.*

#### 6.1.4 Efficacy Findings

##### **Study Patients**

The number of patients originally consented under each of the protocol amendments for phase 2 are shown in the table below.

**Table 6 Patients Consented under each Amendment (Applicant's Table)**

Date of amendment	Amendment	CML-CP (Arm 4, Group A) Primary N=132	CML-CP (Arm 4, Group A) Additional enrollment N=150
17-Mar-2005	Amendment 4 <sup>1</sup> Phase II	131	43
21-July-2005	Amendment 5 Phase II	1	66
9-Nov-2005	Amendment 6 Phase II	0	25
6-Jan-2006	Amendment 7 Phase II	0	11
10-Feb-2006	Amendment 8 Phase II	0	5
24-Feb-2006	Amendment 9 (UK only) Phase II	NA	NA
12-Apr-2006	Amendment 10  Phase II	NA	NA

<sup>1</sup> Amendment 1 through 3 were for Phase I patients only.

Source: Table 10-1, CSR CAMN107A2101E2

### **Dose Selection**

The dose for the pivotal studies was selected on the basis of data from the Phase 1 portion of Study 2101. Dose-response and concentration-response were analyzed for CML-AP patients in Phase 1a Study 2101. Patients in Study 2101 were treated with nilotinib in a once daily regimen with doses ranging from 50 to 1200 mg, or in a twice daily regimen of 400 mg or 600 mg.

Response data from the initial dose groups of patients with CML-AP in Phase 1a Study 2101 were pooled based on pharmacokinetic exposures (AUC) (1) 50 - 200 mg once daily (lower exposure groups) (2) 400 mg once daily to 1200 mg once daily (mid exposure groups) and the higher exposure groups, (3) 400 mg twice daily and (4) 600 mg twice daily. In groups 1, 2, 3, and 4, the percentage of CML-AP patients achieving best hematologic response was, respectively, 13%, 41%, 64%, and 78% (cycle 1) and 38%, 50%, 70%, and 78% (cycle 2). Time to first hematologic response was 76, 87, 43, and 29 days, respectively, and time to best response was 227, 130, 90, and 86 days, respectively. The concentration-response data suggested an efficacy benefit from dosing strategies aimed at achieving the highest tolerable systemic exposure to nilotinib and supported the use of 400 mg twice daily.

Nilotinib serum trough levels at 400 mg twice daily in patients (1800 nM), which exceeded levels observed at the same total daily dose of 800 mg once daily (990 nM), were above the IC<sub>50</sub> of cellular phosphorylation of Bcr-Abl (20-60 nM) and 32 of 33 Bcr-Abl kinase mutants (30-400 nM).

## Data cut off

**Table 7 Data Cut-offs for the Ongoing Efficacy Studies (Applicant's Table)**

Study No./ data cutoff date	Patient population	Purpose	n (total*)	Dose of nilotinib
<b>Pivotal Phase II efficacy and safety trials</b>				
ARM 4, Group A Study 2101E2 Pivotal Phase II trial 04 May 2006	Imatinib-resistant/intolerant Ph+ CML in CP, No prior TKI treatment except imatinib (Gr A)	safety, efficacy, PK, PD	132 efficacy and safety 150 safety only	400 mg b.i.d., (may be dose-escalated to 600 mg b.i.d)
ARM 3, Group A Study 2101E1 Pivotal Phase II trial 23 May 2006	Imatinib-resistant/intolerant Ph+ CML in AP, No prior TKI treatment except imatinib (Gr A)	safety, efficacy, PK, PD	64 efficacy and safety 25 safety only	400 mg b.i.d., (may be dose-escalated to 600 mg b.i.d)
<b>Phase IA MTD-determining trial (supportive efficacy; blood level/response; safety)</b>				
Study 2101 Phase IA trial 03 Mar 2006	Imatinib-resistant CML in CP, AP, and BC; and Ph+ ALL	safety, PK, preliminary efficacy, PD	119 total (17 CP) (46 AP)	dose-escalation; 50 mg q.d. - 1200 mg q.d; 400 mg b.i.d., 600 mg b.i.d.

Source: Table 1-1, Clinical Development AMN107

## 120-Day Efficacy Update

The 120-day efficacy update was in conjunction with the 120-Day Safety Update Report. The additional patients enrolled were 148 CML-CP and 41 CML-AP patients enrolled after the first 132 CML-CP and 64 CML-AP patients. The cut-off dates for inclusion of efficacy data in the update were 4 September 2006 for CML-CP and 23 September 2006 for CML-AP.

## Baseline Demographics and Disease Characteristics

### CML-CP

The mean age of CML-CP patients overall was 56 years with a range of 26 to 85 years. The majority of the patients were male (54.5%) and Caucasian (96.2%). Seventy-three percent (72.7%) patients were < 65 years of age. Baseline WHO performance status score was ≤ 2 in all the patients. The demographics are shown in the table below. This table is consistent with the applicant's analysis.

**Table 8 Baseline Demographics in CML-CP Patients (Reviewer's Table)**

<b>Demographics</b>	<b>ITT N=132 (%)</b>
<b>Age (years)</b>	
Mean	56.4
Median	58.0
SD	13.1
Range	26-85
<b>Age Distribution</b>	
Age < 65	96 (72.7)
< 35	9 (6.8)
≥ 35 - < 55	42 (31.8)
≥ 55- < 65	45 (34.1)
Age ≥ 65	36 (27.3)
<b>Gender</b>	
Male	72 (54.5)
Female	60 (45.5)
<b>Race</b>	
Caucasian	127 (96.2)
Black	3 (2.3)
Asian (Oriental)	2 (1.5)
<b>Weight (kg)</b>	
Mean	77.6
Median	76.8
SD	14.7
Range	43-117.5
Missing	2 (1.5)
<b>WHO performance status</b>	
Grade 0	95 (72.0)
Grade 1	36 (27.3)
Grade 2	1 (0.8)

Source: A\_DMG.xpt; A\_IDENT.xpt

**120-Day Update**

**CML-CP**

The demographics were similar to that described above. The reviewer agrees with the applicant's assessments shown below.

**Table 9 Baseline Demographics in CML-CP Patients 120-Day Update (Applicant's Table)**

<b>No prior TKI except imatinib</b>			
<b>Demographic variable</b>	<b>Primary enrollment N=132</b>	<b>Additional enrollment N=148</b>	<b>Total N=280</b>
<b>Age (years)</b>			
N	132	148	280
Mean ± SD	56.7 ± 13.06	56.5 ± 13.52	56.6 ± 13.29
Median	58.5	58.0	58.0
min – max	26.0 – 85.0	21.0 – 82.0	21.0 – 85.0
<b>Age category (n(%))</b>			
<35 years	9 (6.8)	10 (6.8)	19 (6.8)
≥ 35 - < 55 years	41 (31.1)	49 (33.1)	90 (32.1)
≥ 55 - < 65 years	44 (33.3)	43 (29.1)	87 (31.1)
≥ 65 years	38 (28.8)	46 (31.1)	84 (30.0)
<b>Sex (n (%))</b>			
Male	74 (56.1)	70 (47.3)	144 (51.4)
Female	58 (43.9)	78 (52.7)	136 (48.6)
<b>Race (n (%))</b>			
Asian (Oriental)	2 (1.5)	2 (1.4)	4 (1.4)
Black	3 (2.3)	11 (7.4)	14 (5.0)
Caucasian	127 (96.2)	131 (88.5)	258 (92.1)
Other	0 (0.0)	3 (2.0)	3 (1.1)
Pacific islander	0 (0.0)	1 (0.7)	1 (0.4)
<b>Weight (kg)</b>			
N	130	147	277
Mean ± SD	77.6 ± 14.88	79.1 ± 20.62	78.4 ± 18.13
Median	76.8	75.6	76.2
min – max	43.0 – 117.5	46.0 – 165.0	43.0 – 165.0
<b>WHO performance status (n (%))</b>			
Grade 0	95 (72.0)	105 (70.9)	200 (71.4)
Grade 1	36 (27.3)	38 (25.7)	74 (26.4)
Grade 2	1 (0.8)	4 (2.7)	5 (1.8)
Missing	0 (0.0)	1 (0.7)	1 (0.4)

Source: Table 4-1, SCE 120-Day Update

### Baseline Disease Characteristics

There was a discrepancy seen between the applicant demographics in dataset A\_PT.M.xpt and the FDA review in the number of patients who had received prior interferon (91 patients vs. 53 patients) and in the patients who had received with prior transplant (14 vs. 1). Prior interferon in dataset includes interferon, interferon alpha, peginterferon alpha 2a, interferon alfa-2b and peginterferon alfa-2b. Prior transplants include various descriptions bone marrow transplant, peripheral stem cell transplant, autologous transplant, allogeneic transplant and autograft. A query was sent to the sponsor and they agreed that when accounting for all types of prior interferon usage, 91 patients had received prior therapy with an interferon agent. They also agreed that when accounting for prior transplantation (both stem cell and non stem cell), 14 patients had prior transplant.

**Table 10 Baseline Disease Characteristics CML-CP (Reviewer's Table)**

<b>Disease Characteristic</b>	<b>ITT N=132 (%)</b>
<b>Baseline chromosome Ph +</b>	
Yes	132 (100)
<b>Prior Treatment</b>	
Imatinib	132 (100)
TKI other than imatinib	0
Hydroxyurea	110 (83.3)
Interferon	91 (68.9)
Anagrelide	7 (5.3)
Transplant	14 (10.6)
<b>Time since first diagnosis of CML (months)</b>	
Mean	67.5
Median	57.3
Range	5.4-279
<b>Imatinib Resistance/Intolerance</b>	
Imatinib-resistant	91 (68.9)
Imatinib-intolerant	41 (31.1)
<b>Prior Imatinib Dose</b>	
< 600 mg	34 (25.8)
600 - < 800 mg	42 (31.8)
≥ 800 mg	55 (41.7)
<b>Baseline BM Blasts</b>	
≥ 50 %	0
missing	20 (15.2)
<b>BCR-ABL mutations</b>	

Yes	21 (61.8)
No	13 (9.8)
Missing	98 (74.2)
<b>Baseline CHR</b>	
Yes	46 (34.8)
No	86 (65.2)
<b>Prior Best Response to CML-CP</b>	
Cytogenetic response	79 (59.8)
Complete hematologic response but no cytogenetic response	38 (28.8)
Never achieved CHR	11 (8.3)
missing	4 (3.0)

Source: A\_DMKG.xpt; A\_IDENT.xpt; A\_PTM.xpt

**120-Day Update**

Baseline demographic characteristics were similar as described above. The reviewer agrees with the applicant's assessment as shown below.

**Table 11 Baseline Disease Characteristics CML-CP 120-Day Update (Applicant's Table)**

**Appears This Way  
On Original**

<b>No prior TKI except imatinib</b>			
<b>Disease history</b>	<b>Primary enrollment N=132</b>	<b>Additional enrollment N=148</b>	<b>Total N=280</b>
<b>Baseline CHR</b>			
Yes	46 (34.8)	49 (33.1)	95 (33.9)
No	86 (65.2)	99 (66.9)	185 (66.1)
<b>Time since first diagnosis of CML (months)</b>			
N	132	148	280
Median	57.7	56.2	57.3
<b>Number (%) of patients</b>			
Imatinib-resistant	91 (68.9)	103 (69.6)	194 (69.3)
Imatinib-intolerant	41 (31.1)	45 (30.4)	86 (30.7)
<b>Prior highest imatinib dose (n (%))</b>			
< 600 mg	34 (25.8)	43 (29.1)	77 (27.5)
≥ 600 mg - < 800 mg	44 (33.3)	47 (31.8)	91 (32.5)
≥ 800 mg	53 (40.2)	58 (39.2)	111 (39.6)
Missing	1 (0.8)	0 (0.0)	1 (0.4)
<b>Prior non-drug: organ transplants</b>			
	14 (10.6)	8 (5.4)	22 (7.9)
<b>Prior interferon*</b>			
	92 (69.7)	92 (62.2)	184 (65.7)
<b>Baseline BM blasts ≥50%</b>			
	0 (0.0)	0 (0.0)	0 (0.0)
<b>BCR-ABL mutations</b>			
	<b>Baseline CHR</b>	<b>Baseline Not CHR</b>	<b>Total</b>
N**	37	64	101
n (%)	10 (27.0)	35 (54.7)	45 (44.6)

Patients who are both imatinib-resistant and imatinib-intolerant are included under imatinib-resistant.

\*Category of "prior interferon" includes interferon, interferon α, interferon α-2a, interferon α-2b, interferon γ, interferons, peginterferon α-2a, and peginterferon α-2b.

\*\*N= number of primary enrollment patients in the ITT primary population with baseline mutation analysis performed. Baseline mutational analysis was not performed for the primary enrollment patients in the conventional ITT population or for the patients in the additional enrollment.

Source: Table 4-2, SCE 120-Day Update

### **CML-AP**

The mean age of CML-AP patients overall was 59 years with a range of 24 to 79 years. The majority of the patients were male (53.1%) and Caucasian (85.9%). Sixty six percent (65.7%) patients were < 65 years of age. Baseline WHO performance status score was ≤ 2 in all the patients, except one. The demographics are shown in the table below. This table is consistent with the applicant's analysis.

**Table 12 Baseline Demographics in CML-AP Patients (Reviewer's Table)**

<b>Demographics</b>	<b>ITT N=64 (%)</b>
<b>Age (years)</b>	
Mean	58.8
Median	61.0
SD	12.9
Range	24-79
<b>Age Distribution</b>	
Age < 65	42 (65.7)
< 35	4 (6.3)
≥ 35 - < 55	13 (20.3)
> 55- < 65	25 (39.1)
Age ≥ 65	22 (34.4)
<b>Gender</b>	
Male	34 (53.1)
Female	30 (46.9)
<b>Race</b>	
Caucasian	55 (85.9)
Black	6 (9.4)
Asian	3 (4.7)
<b>Weight (kg)</b>	
Mean	76.4
Median	78.7
SD	15.6
Range	46-114.5
Missing	1
<b>WHO performance status</b>	
Grade 0	28 (43.8)
Grade 1	30 (46.9)
Grade 2	5 (7.8)
Grade > 2	1 (1.6)

Source: A\_DMKG.xpt; A\_IDENT.xpt

**120-Day Efficacy Update**

The demographic data were similar to that described above except for the age distribution. There was a greater percentage of patients in the age category of ≥ 35 to < 55 years in the additional

enrollment and a greater percentage of patients in the age category of  $\geq 55$  to  $< 65$  years in the primary enrollment. The reviewer agrees with the applicant's assessment as shown below.

**Table 13 Baseline Demographics in CML-AP Patients 120-Day Update (Applicant's Table)**

<b>No prior TKI except imatinib</b>			
<b>Demographic variable</b>	<b>Primary enrollment N=64</b>	<b>Additional enrollment N=41</b>	<b>Total N=105</b>
<b>Age (years)</b>			
N	64	41	105
mean $\pm$ SD	58.4 $\pm$ 13.02	54.3 $\pm$ 13.54	56.8 $\pm$ 13.32
Median	60.0	51.0	59.0
min – max	24.0 – 79.0	30.0 – 78.0	24.0 – 79.0
<b>Age category (n (%))</b>			
<35 years	4 (6.3)	2 (4.9)	6 (5.7)
$\geq 35$ - $< 55$ years	14 (21.9)	22 (53.7)	36 (34.3)
$\geq 55$ - $< 65$ years	25 (39.1)	5 (12.2)	30 (28.6)
$\geq 65$ years	21 (32.8)	12 (29.3)	33 (31.4)
<b>Sex (n (%))</b>			
Male	34 (53.1)	23 (56.1)	57 (54.3)
Female	30 (46.9)	18 (43.9)	48 (45.7)
<b>Race (n (%))</b>			
Asian	3 (4.7)	5 (12.2)	8 (7.6)
Black	6 (9.4)	1 (2.4)	7 (6.7)
Caucasian	55 (85.9)	33 (80.5)	88 (83.8)
Other	0 (0.0)	2 (4.9)	2 (1.9)
<b>Weight (kg)</b>			
N	63	41	104
mean $\pm$ SD	76.7 $\pm$ 15.69	71.4 $\pm$ 17.83	74.6 $\pm$ 16.69
Median	80.1	70.0	74.0
min – max	46.0 – 114.5	43.0 – 123.0	43.0 – 123.0
<b>WHO performance status (n (%))</b>			
Grade 0	27 (42.2)	25 (61.0)	52 (49.5)
Grade 1	31 (48.4)	15 (36.6)	46 (43.8)
Grade 2	5 (7.8)	1 (2.4)	6 (5.7)
Grade >2	1 (1.6)	0 (0.0)	1 (1.0)

Source: Table 4-6, SCE, 120-Day Update

### Baseline Disease Characteristics

There was a discrepancy seen between the applicant demographics in dataset A\_PT.M.xpt and the FDA review in the number of patients who had received prior interferon and in the patients who had received with prior transplant. Prior interferon in dataset includes interferon, interferon alpha, peginterferon alpha 2a, and interferon alfa-2b. Prior transplants include autologous transplant and allogeneic transplant. A query was sent to the sponsor and they agreed that when accounting for all types of prior interferon usage, 37 patients had received prior therapy with an interferon agent. They also agreed that when accounting for prior transplantation (both stem cell and non stem cell), 3 patients had prior transplant.

**Table 14 Baseline Disease Characteristics CML-AP (Reviewer's Table)**

<b>Disease Characteristic</b>	<b>ITT N=64 (%)</b>
<b>Baseline chromosome Ph +</b>	
Yes	64 (100)
<b>Prior Treatment</b>	
Imatinib	64 (100.0)
TKI other than imatinib	0
Hydroxyurea	57 (89.1)
Interferon	37 (57.8)
Anagrelide	10 (15.6)
Stem cell transplant	3 (4.7)
<b>Time since first diagnosis of CML (months)</b>	
Mean	79.9
Median	74.7
Range	2.3-302.5
<b>Time since first diagnosis of CML AP (months)</b>	
Mean	13.7
Median	1.9
Range	0-107.5
<b>Imatinib Resistance/Intolerance</b>	
Imatinib-resistant	52 (81.3)
Imatinib-intolerant	12 (18.8)
<b>Prior Imatinib Dose</b>	
< 600 mg	11 (17.2)
600 - < 800 mg	52 (81.3)
≥ 800 mg	1 (1.6)

<b>Baseline BM Blasts</b>	
≥ 50 %	0
Missing	12 (18.8)
<b>BCR-ABL mutations</b>	
Yes	11 (17.2)
No	3 (4.7)
Missing	50 (78.1)
<b>Prior Best Response</b>	
Complete hematologic response	4 (6.3)
Return to chronic	2 (3.1)
Cytogenetic response	8 (12.5)
None	33 (51.6)
Missing	17 (26.6)

Source: A\_DM.G.xpt; A\_IDENT.xpt; A\_PTM.xpt

### **120-Day Update**

The baseline disease characteristics were similar to that described above except for the percentages of imatinib-resistant vs. imatinib-intolerant patients. There was a greater percentage of imatinib-intolerant patients in the additional enrollment (22%) than in the primary enrollment (17.2%). The reviewer agrees with the applicant's assessment as shown in the table below.

**Table 15 Baseline Disease Characteristics CML-AP (Applicant's Table)**

**Appears This Way  
On Original**

No prior TKI except imatinib	Primary enrollment N=64	Additional enrollment N=41	Total N=105
<b>Disease history</b>			
<b>Time since first diagnosis of CML (months)</b>			
N	64	41	105
Median	77.4	74.0	76.1
minimum - maximum	2.2 – 252.2	4.2 0 298.2	2.2 – 252.2
<b>Number (%) of patients</b>			
Imatinib-resistant	53 (82.8)	32 (78.0)	85 (81.0)
Imatinib-intolerant	11 (17.2)	9 (22.0)	20 (19.0)
<b>Prior highest imatinib dose (n (%))</b>			
<600 mg	11 (17.2)	6 (14.6)	17 (16.2)
≥600 mg - <800 mg	20 (31.3)	13 (31.7)	33 (31.4)
≥ 800 mg	33 (51.6)	22 (53.7)	55 (52.4)
<b>Prior non-drug: organ transplants</b>			
	4 (6.3)	4 (9.8)	8 (7.6)
<b>Prior interferon*</b>			
	37 (57.8)	24 (58.5)	61 (58.1)
<b>Baseline BM blasts ≥50%</b>			
	0 (0.0)	0 (0.0)	0 (0.0)
<b>BCR-ABL mutations</b>			
N**	46	--	--
N (%)	26 (56.5)	--	--

Patients who are both imatinib-resistant and imatinib-intolerant are included under imatinib-resistant.

\*Category of "prior interferon" includes interferon, interferon α, interferon α-2a, interferons, and peginterferon α-2a.

\*\*N= number of patients with baseline mutation analysis performed. Baseline mutational analysis was not performed for the primary enrollment patients in the conventional ITT population or for the patients in the additional enrollment.

Source: Table 4-7, SCE, 120-Day Update

## **Protocol Exclusions**

### **CML-CP**

Out of the initial 132 patients, 44 (33.3%) patients were excluded due to the reasons shown in the table below.

Five (3.8%) patients had zero cells at baseline and were not evaluable for a major cytogenetic response

Two patients (0304\_04004 and 0401\_04004) had initial bone marrow assessments done on days 1 and 2 respectively. These were not considered to be at baseline which was defined as 14 days prior to start of cycle 1.

Patient 0301\_04007 has less than 20 metaphases at baseline, but FISH showed 100% Ph+ cells and was included for efficacy.

**Table 16 Reasons for Exclusion CML-CP Primary Population (N=132) (Reviewer's Table)**

<b>Reason for Exclusions</b>	<b>Patient ID #</b>	<b>N (%)</b>	<b>Comments</b>
Patients not in chronic phase	0304_04005 0304_04007 0304_04011 0305_04007 0401_04004 0502_04004 0502_04005 0508_04003 0512_04001 0603_04002	10 (7.6)	Not evaluable for cytogenetic or hematologic response
Patients with zero cells at baseline cytogenetic analysis	0303_04002 0305_04001 0305_04007 0350_04008 0402_04001	5 (3.8)	Not evaluable for cytogenetic response
Missing or inadequate baseline bone marrow with < 20 metaphases	0301_04002 0301_04003 0301_04007 0304_04005 0305_04005 0305_04019 0306_04002 0306_04003 0306_04004 0350_04001 0350_04002 0350_04003 0350_04010 0351_04001 0351_04002 0351_04003 0351_04004 0351_04006	27 (20.5)	Not evaluable for cytogenetic response

	0401_04001 0501_04003 0502_04001 0502_04002 0603_04001 0603_04002 0702_04004 0702_04007 0801_04002 0901_04001		
Absence of bone marrow at baseline study days	0304_04004 0401_04004	2 (1.5)	Not evaluable for cytogenetic and hematologic response

Source: A\_DMKG, A\_BMA, A\_FSH, A\_EFFVIS.xpt

Out of the 148 additional patients, 23 (15.5%) patients were excluded. None of the 21 patients with missing or inadequate bone marrow cytogenetics has a FISH with 100% Ph+ cells at baseline.

Thus a total of 67 (23.9%) patients in the primary and additional patient population (N=280) were not evaluable for the primary efficacy endpoint of cytogenetic response.

**Table 17 Reasons for Exclusion CML-CP Additional Population (N=148) (Reviewer's Table)**

Reason for Exclusions	Patient ID #	N (%)	Comments
Missing or inadequate (< 20 metaphases) baseline bone marrow cytogenetics	0302_04010	18 (12.2)	Not evaluable for cytogenetic response
	0305_04016		
	0351_04007		
	0502_04014		
	0505_04002		
	0524_04001		
	0601_04006		
	0603_04006		
	0605_04008		
	0606_04004		
	0702_04011		
	0801_04007		
	0809_04001		
	0809_04002		
	0809_04003		
	0809_04004		
	0809_04005		

	0809_04006		
Not in chronic phase	0201_04001 0211_04003 0302_04010 0305_04011 0305_04012 0503_04008 0512_04001 0516_04004 0520_04002 0523_04001 0601_04006 0610_04001 0801_04007	13 (8.8)	Not evaluable for cytogenetic or hematologic response
Absence of BM cytogenetic assessments at baseline	0609_04001 0811_04005 0814_04003	3 (2.0)	Not evaluable for cytogenetic response
Patients with zero cells at baseline cytogenetic analysis	0201_04001 0202_04006	2 (1.4)	Not evaluable for cytogenetic response

Source: A\_DMG, A\_BMA, A\_FSH, A\_EFFVIS.xpt

### CML-AP

In the primary 64 patients, 14 (21.9%) patients were excluded from the evaluation of a hematologic response.

**Table 18 Reasons for Exclusion CML-AP (N=64) (Reviewer's Table)**

Reasons for Exclusion	Patient ID #	N (%)	Comments
Patients not in accelerated phase	0350_03003 0503_03005	2 (3.1)	Not evaluable for cytogenetic or hematologic response
Absence of bone marrow blast assessments at baseline	0301_03007 0303_03002 0304_03002 0308_03001 0350_03003 0503_03005 0504_03003 0504_03004	10 (15.6)	Not evaluable for hematologic response

	0504_03005 0860_03001		
CHR at baseline	0305_03007 0401_03002 0519_03002 0802_03001	4 (6.3)	Not evaluable for hematologic response
Inadequate bone marrow assessments at baseline (< 20 metaphases)	0301_03004 0305_03007 0603_03001 0860_03001	4 (6.3)	Not evaluable for cytogenetic response
Absence of bone marrow cytogenetic assessment at baseline	0301_03007 0302_03002 0303_03002 0308_03001 0350_03001 0350_03002 0350_03003 0350_03004 0350_03005 0401_03002 0401_03004 0501_03002 0501_03004 0501_03006 0502_03003 0504_03001 0504_03005 0504_03006 0605_03001 0801_03001 0804_03002 0809_03001 0901_03001	23 (35.9)	Not evaluable for cytogenetic response

Source: A\_DMG, A\_BMA, A\_FSH, A\_EFFVIS.xpt

In the additional 41 patient population, six (14.6%) patients were not evaluable for a hematologic response.

**Table 19 Reasons for Exclusion CML-AP Additional Patients (N=41) (Reviewer's Table)**

Reasons for Exclusion	Patient ID #	N (%)	Comments
Absence of bone marrow blast assessments	0301_03009	6 (14.6%)	Not evaluable

at baseline	0305_03009 0811_03004 0872_03003 0872_03004 0872_03005		for hematologic response
Inadequate bone marrow assessments at baseline (< 20 metaphases)			Not evaluable for cytogenetic response
Absence of bone marrow cytogenetic assessment at baseline			Not evaluable for cytogenetic response

Source: A\_DMG, A\_BMA, A\_FSH, A\_EFFVIS.xpt

*Reviewer's Comments:*

*The reviewer had a concern based on the numbering of patients that the patient numbers may not be assigned sequentially. The applicant clarified that the patient numbers were assigned sequentially.*

*The reviewer adjudicated responses based on these exclusions. Adjudicated responses were discussed with the applicant.*

*In a response to FDA questions dated 6/28/07, the applicant stated that "it is not unusual in clinical studies of patients with CML for such parameters to occasionally not be recorded" in reference to the "bone marrow blast parameters". The reviewer does not agree with this statement as the bone marrow blasts should not be missing because the most important reason to check a leukemia marrow is usually to see the percent blasts. Also, it does not reflect standard clinical practice.*

**Patient Disposition**

**CML-CP**

Data cut-off for the analyses presented was May 4, 2006.

The table below presents the patient disposition for the 132 efficacy patients. Adverse events were the most common cause for discontinuation of treatment. Specific reasons for all were not available. Although 26 patients were recorded to have discontinued due to adverse events in the dataset A\_CMP.xpt, only 12 explanations of the abnormal test were given, of which the most common was grade 3 and greater thrombocytopenia. Two of the patients were recorded as having disease progression had adverse events. Two of the patients who withdrew consent went

for bone marrow transplantation. The patient with abnormal ECG at baseline should not have been entered into the trial.

**Table 20 Patient Disposition CML-CP (Reviewer's Table)**

<b>Patient Disposition</b>	<b>N=132 (%)</b>
Ongoing at time of cut-off	82 (62.1)
Discontinued treatment	50 (37.9)
<b>Reasons for Treatment Discontinuation</b>	
Adverse events	26 (19.7)
thrombocytopenia (5)	
thrombocytopenia & neutropenia (1)	
neutropenia (1)	
patient did not wish to continue due to AE (1)	
increased bilirubin/liver toxicity (2)	
skin rash (1)	
myocardial infarction hospitalization (1)	
Disease Progression	15 (11.4)
pancreatitis (1)	
neutropenia grade 4 (1)	
Withdrew consent	5 (3.8)
patient went to BMT (2)	
lack of response (1)	
patient will have treatment done locally (1)	
Death	2 (1.5)
myocardial infarction (1)	
multi-organ failure (1)	
Protocol violation	1 (0.8)
Abnormal ECG at baseline (1)	
Lost to follow-up	1 (0.8)

Source: A\_CMP.xpt

### **120-Day Update**

The most frequent reasons for discontinuation were adverse events and disease progression.

### **CML-AP**

Patient Disposition (Reviewer's Table)

<b>Patient Disposition</b>	<b>N=132 (%)</b>
----------------------------	------------------

Ongoing at time of cut-off	33 (51.6)
Discontinued treatment	31 (48.4)
Reasons for Treatment Discontinuation	
Disease Progression	14 (21.9)
Adverse events	8 (12.5)
ongoing drug intolerance (1)	
unable to discontinue his amiodarone (1)	
developed rash after taking 2 doses of drug (1)	
Pancreatitis (1)	
myocardial infarction and progressive disease (1)	
repeated grade 3 thrombocytopenia and neutropenia (1)	
Withdrew consent	4 (6.3)
Death	2 (3.1)
Intracerebral hemorrhage (1)	
Cardiac failure (1)	
Abnormal laboratory values	1 (1.6)
Lost to follow-up	1 (1.6)
Administrative problems	1 (1.6)

Source: A\_CMP.xpt

### **120-Day Update**

The most frequent reasons for discontinuation were adverse events and disease progression.

### **Efficacy Analyses**

#### **CML-CP**

The primary efficacy analysis was performed based on the first 132 CML-CP patients who had either completed 6 months of treatment or discontinued the study.

#### **Primary Efficacy Analysis: Major Cytogenetic Response (MCyR)**

In the FDA analyses taking into account bone marrow cytogenetics at baseline only, 94 (71.2%) patients were eligible for cytogenetic response assessments. 38 patients were adjudicated with major protocol violations and considered not assessable for the primary efficacy analyses of a MCyR. The MCyR was 19.7% and the confirmed MCyR was 15.9% based on adjudicated FDA responses. The discrepancies with the sponsor's assessments are the following:

1. Patients whose baseline BM assessment showed a response and whose chromosomes remained in one response category was considered unchanged for response. Thus patients who had 1%-35% cells at baseline (defined as partial response) and had changes which remained between 1% to 35% during post-baseline assessments were considered to have had no response. There was no percentage decrease defined in the protocol to

consider a partial response. Of note, 130 (98.5 %) patients started out at baseline in partial response (0-35% chromosomes) and six patients (4.5%) had a complete cytogenetic response at baseline (0% cells).

2. Although the protocol states that FISH would be used if bone marrows were not available, it is not clear that bone marrow aspirate/biopsies were repeated in these patients. The sponsor also considers either a bone marrow or a FISH response as a response if any one was available. In this review, only bone marrow cytogenetic assessments were considered for the assessment of response as FISH has not been validated for response assessments.

**Table 21 Cytogenetic Response CML-CP (Reviewer’s Table)**

Cytogenetic Response (CyR)	Applicant Analysis	FDA Analyses					
	CyR BM or FISH N=132 (%)	CyR BM N=132 (%)		CyR BM or FSH (baseline) N=132 (%)		CyR BM or FISH (baseline & response) N=132 (%)	
		Unconfirmed	Confirmed	Unconfirmed	Confirmed	Unconfirmed	Confirmed
Major CyR (Complete + Partial)	55 (41.7)	34 (25.8)	24 (18.2)	28 (21.2)	18 (13.0)	37 (27.9)	27 (20.4)
Complete	33 (25.0)	24 (18.2)	21 (15.9)	25 (18.9)	17 (12.9)	30 (22.7)	25 (18.9)
Partial	22 (16.7)	10 (7.6)	3 (2.3)	3 (2.3)	1 (0.8)	7 (5.3)	2 (1.5)
Minor	10 (7.6)	5 (3.8)		0		1 (0.8)	
Minimal	15 (11.4)	12 (9.1)		0		0	
None	21 (15.9)	25 (18.9)					
No change				78 (59.1)		68 (52.3)	

BM: bone marrow cytogenetics

### **120-Day Efficacy Update**

As of the cut-off date for the 120-day efficacy update, the initial 132 CML-CP patients had completed 10 months for CML-CP of treatment or discontinued the study. The criteria for efficacy responses in the updated data were the same as that used in the initial submission. The population analysed by the applicant was the “Conventional ITT” population which consisted of all patients who were assessed for their response irrespective of any major protocol violation and actual observed responses of these major protocol violators were considered.

#### *Reviewer’s Comments:*

*A conventional ITT population was not considered in this single-arm Phase 2 study. The reviewer adjudicated responses based on patients who were excluded if they were not in the intended population as described above in the primary analysis.*

### **Major Cytogenetic Response (MCyR)**

**Additional Enrollment**

There were 148 additionally enrolled patients in the CML-CP population. Due to the significant number of patients included, the reviewer analyzed and adjudicated the additionally enrolled patients in a similar manner to the primary population. Thus the final responders are based on the total of primary and additional patients of 280 patients.

The reviewer noted that the patient # 0502\_04012 appeared in both the initial and additional populations in the updated datasets. The applicant was queried and gave the following explanation: "There were two CML-CP patients who had been included in Group B (0303-04001 and 0606-04002) in the initial submission, that were reassigned to Group A for the SCE 120-day update due to changes in their previous TKI history. Due to their enrollment dates, they became part of the primary enrollment of 132 CML-CP Group A patients in the SCE 120-day update by replacing the two last enrolled Group A patients (0502-04012 and 0512-04001) who had been included in the primary enrollment in the initial submission. These two replaced patients (0502-04012 and 0512-04001) now became part of the Group A additional enrollment in the SCE 120-day update".

**Table 22 Cytogenetic Response CML-CP 120-Day Update (Reviewer's Table)**

Cytogenetic Response	Applicant Analyses <sup>a</sup>		FDA Adjudicated Analyses <sup>b</sup>			
	Additional Patients N=148 (%)	Primary and Additional Patients N=280 (%)	Additional Patients N=148 (%)		Primary and Additional Patients N=280 (%)	
	Unconfirmed	Unconfirmed	Unconfirmed	Confirmed	Unconfirmed	Confirmed
Major CyR (Complete + Partial)	80 (54.1)	145 (51.8)	53 (35.8)	23 (15.5)	98 (35.0)	53 (18.9)
95% CI	45.7, 62.3	45.8, 57.8			29.4, 40.9	14.5, 24.0
Complete	54 (36.5)	96 (34.3)	36 (24.3)	20 (13.5)	68 (24.3)	42 (15.0)
Partial	26 (17.6)	49 (17.5)	17 (11.5)	3 (2.0)	30 (10.7)	11 (3.9)
Minor	10 (6.8)	22 (7.9)	5 (3.4)		9 (3.2)	
Minimal	20 (13.5)	39 (13.9)	11 (7.4)		21 (7.5)	
None	21 (14.2)	40 (14.3)	27 (18.2)		48 (17.1)	

<sup>a</sup> based on bone marrow or FISH assessments at baseline and for response; based on all ITT patients irrespective of protocol violations

<sup>b</sup> based on bone marrow cytogenetics and on patients with no protocol violations

*Reviewer's Comments:*

1. Since the cytogenetic response criteria are specific cutoffs, patients who are <35% Ph+ at baseline can only achieve a CR to have a valid clinical benefit.
2. Metaphase cytogenetics and FISH are not equivalent, and there is no validation of FISH alone for response in CML.

3. *FISH is not a validated test. For this submission for accelerated approval, a standard test is important towards proving that the test measures the surrogate reasonably likely to clinical benefit. Hence, only bone marrow cytogenetics were reviewed for baseline and response assessments.*

### Applicant's Re-Analysis

The applicant also submitted a re-analysis of the cytogenetic response in the study in CML-CP patients on the same dataset as submitted with the 120-Day Efficacy Update, but ignoring data generated with the FISH method as well as patients who had complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR) at baseline and remained in this response.

For the purpose of the analysis, a subset of 232 patients with adequate cytogenetic data at baseline (with  $\geq 20$  metaphases) was identified. This group of patients represented 82.8% of the study population of 280 patients.

The applicant showed that their baseline demographics and disease characteristics did not differ from the overall study population of 280 patients. The duration of exposure for these 232 patients was also similar to the overall study population. For both, the median exposure was 8.5 months (mean 8.1 months).

The evaluation of major cytogenetic response rate among the 232 patients with  $\geq 20$  metaphases at baseline was based on the following criteria in accordance with the FDA reviewer assessment as described previously:

- Only post-baseline bone marrow cytogenetic assessments with  $\geq 20$  metaphases had been used, but no FISH assessments and no bone marrow assessments with  $< 20$  metaphases
- Patients with PCyR (1-35% Ph+) at baseline were only considered eligible for CCyR (0% Ph+) but not counted as responder if they remained in the PCyR category.
- Patients with CCyR (0% Ph+) at baseline were not counted as responder even though the patients continued to maintain the CCyR post-baseline.

The applicant presented the data as a shift table showing the distribution of patients according to the quality of their baseline cytogenetic data and according to the quality of the response observed during the study. For completeness, the following shift table shows all 280 CML-CP patients who were included in the 120-day update as having at least 6 months of follow-up or had been prematurely discontinued.

**Table 23 Baseline Cytogenetic versus Post-baseline Cytogenetic Response (Applicant's Table)**

Baseline cytogenetics	Post-baseline cytogenetic response								
	CCyR	PCyR	No MCyR	Missing- CCyR	CCyR -CCyR	PCyR -PCyR	CCyR by FISH	PCyR by FISH	Total
BM $\geq 20$ with MCyR	10	0	4	0	4	2	2	0	22

Baseline cytogenetics	Post-baseline cytogenetic response								Total
	CCyR	PCyR	No MCyR	Missing- CCyR	CCyR -CCyR	PCyR -PCyR	CCyR by FISH	PCyR by FISH	
BM ≥ 20 without MCyR	57	27	107	0	0	0	6	13	210
BM <20 & FISH	1	0	3	0	0	0	0	1	5
BM <20 & No FISH	2	2	4	0	0	0	0	0	8
No BM & FISH	2	3	12	0	1	1	2	3	24
No BM & No FISH	0	0	5	3	0	0	2	1	11
<b>Total</b>	<b>72</b>	<b>32</b>	<b>135</b>	<b>3</b>	<b>5</b>	<b>3</b>	<b>12</b>	<b>18</b>	<b>280</b>

BM = Bone marrow

Missing – CCyR = Patients with missing baseline and CCyR post-baseline

CCyR – CCyR = Patients who had CCyR at baseline and remained in CCyR

PCyR – PCyR = Patients who had PCyR at baseline and remained in PCyR

Source: [Post-text supplement 1: Ad hoc Table -- Baseline cytogenetics and post-baseline cytogenetic response (ITT)]

Source: Table 2-1, Response to FDA Questions Document dated 8/15/07

As per the analysis in the 232 CML-CP patients with ≥20 metaphases evaluated at baseline and who had at least 6 months of follow-up or prematurely discontinued (median exposure 8.5 months, 25-75<sup>th</sup> percentiles 5 to 11 months), a total of 94 patients (40.5%) achieved MCyR (95% CI: 34.1 – 47.1) and 67 patients (28.9%) achieved CCyR.

The FDA adjudicated analysis in the 232 CML-CP patients with ≥ 20 metaphases evaluated at baseline and who had at least 6 months of follow-up, a total of 92 (39.7%) patients achieved an unconfirmed MCyR (95% CI: 33.3, 46.3) and 53 (22.8%) patients achieved a confirmed MCyR (95% CI: 14.5, 24). A confirmed complete cytogenetic response was seen in 42 (18%) patients.

A comparison of the applicant and FDA analyses are shown below.

**Table 24 Best Cytogenetic response in CML-CP Re-Analyses (Reviewer's Table)**

**Appears This Way  
On Original**

	Applicant's Analysis N=232 N (%)	FDA Adjudicated Analysis Unconfirmed N=232 N (%)	FDA Adjudicated Analysis Confirmed N=232 N (%)
<b>Major response (Complete + Partial)</b>	<b>94 (40.5)</b>	<b>92 (39.7)</b>	<b>53 (22.8)</b>
95% CI	34.1-47.1	33.3, 46.3	17.6, 28.7.0
Complete response (CCyR)	67 (28.9)	65 (28.0)	42 (18.1)
Partial response (PCyR)	27 (11.6)	27 (11.6)	11 (4.7)

Source: Table 2-2, Response to FDA Questions Document dated 8/15/07; A\_BMA.xpt

*Reviewer's Comments:*

*Although the reviewer considers confirmed major cytogenetic responses to be more meaningful than unconfirmed cytogenetic responses, in accordance with the precedence in the dasatinib label, unconfirmed cytogenetic responses can be included in the label. The confirmed complete cytogenetic responses should also be included.*

**Secondary Efficacy Analysis**

**Duration of MCyR (120-Day Efficacy Update)**

The applicant analyzed duration of MCyR according to the protocol defined as time from the date of first occurrence of the response to the earliest date of the following: loss of response, progression to AP or BC, discontinuation due to AE, lab abnormality, PD, or death. For patients without any of the above events, duration of MCyR was censored at date of discontinuation or date of data cut-off for patients still on treatment. For patients for whom none of these events were reported, duration of response was censored at the cut-off date or at the discontinuation date (for patients who discontinued due to other reasons).

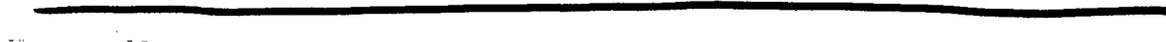
The FDA analysis of duration utilized the applicant's definition per protocol. The median duration was not reached.

**Table 25 Duration of Response in Responders in Primary and Additional Patients Enrolled CML-CP (Reviewer's Table)**

Duration MCyR CML-CP	Primary and Additional Patients N=280
Number of Responders	92
Number censored	71 (79.8%)
Duration of response (months)	
25 percentile w 95% CI	10.61 (5.55,*)
50 percentile w 95% CI	*
75 percentile w 95% CI	*

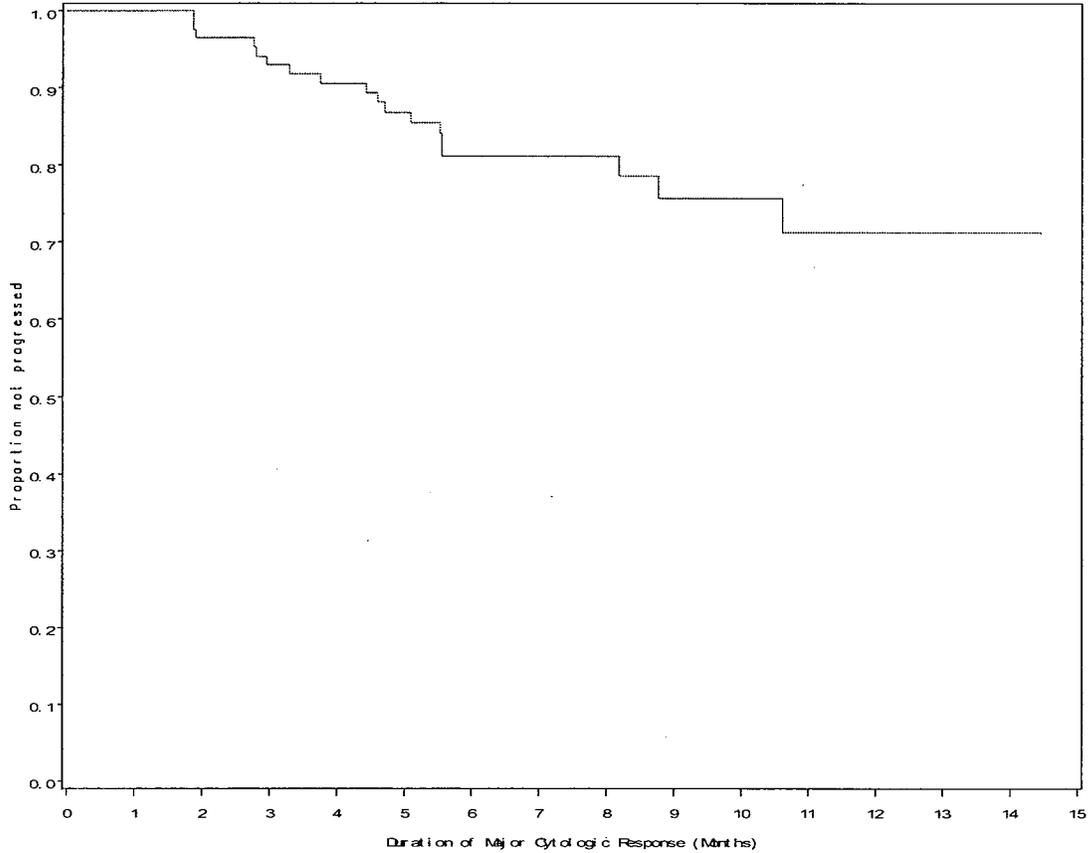
\* could not be estimated due to more than 70% censored

The Kaplan-Meier curve below displays the duration of MCyR in the 92 patients. The median duration of response has not been reached. The longest duration seen was 14.5 months.



**Figure 1** Duration MCyR CML-CP K-M Curve (Reviewer's Figure)

**Appears This Way  
On Original**



### **Time to major cytogenetic response**

In the primary and additional patients with at least 6 months of follow-up, the median time to first MCyR was 2.8 months.

### **Loss of MCyR**

In the 280 patients with at least 6 months of follow-up, loss of MCyR was observed in 25 (26.9%) of the 92 patients who had an unconfirmed MCyR.

### **Complete Hematologic Response**

### **120-Day Efficacy Update**

Complete hematologic response was observed in 92 patients (49.7%) compared to the applicant's 74.1% of the 185 patients in the primary and additional population who were without CHR at baseline and therefore assessable for CHR.

**Table 26 Complete Hematologic Response in Patients without CHR at baseline CML-CP (Reviewer's Table)**

<b>Hematologic Response</b>	<b>Applicant Primary and Additional Patients N=280 (%)</b>	<b>FDA Primary and Additional Patients N=280 (%)</b>
<b>Baseline not CHR</b>	185 (66)	185 (66)
<b>CHR</b>	137 (74.1)	92 (49.7)
<b>95% CI</b>	67.1, 80.2	42.3, 57.2

The median duration was not reached.

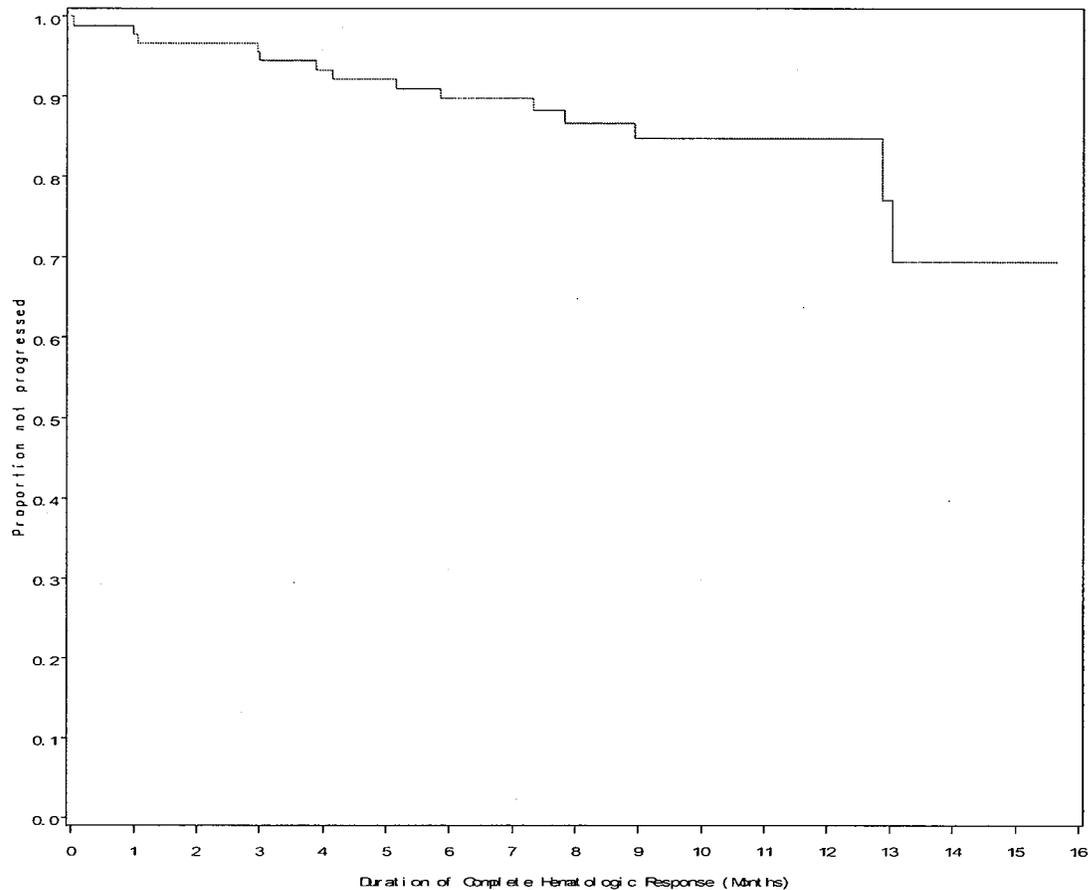
**Table 27 Duration of CHR in Responders CML-CP**

	<b>FDA adjudicated CHR N=185</b>
<b>Number of responders</b>	92
<b>Number censored</b>	76 (84.4%)
<b>Median 95% CI</b>	*(13.4, *)
<b>25 percentile 95% CI</b>	13.4 (12.88,*)
<b>75 percentile 95% CI</b>	*

\*could not be estimated due to more than 70% censored

The Kaplan-Meier curve below displays the duration of CHR in the 92 patients. The longest duration seen was 15.6 months.

**Figure 2 Duration of CHR K-M Curve (Reviewer's Figure)**



### Time to CHR

The median time to CHR for the 92 patients without a CHR at baseline of the 280 patients with at least 6 months of follow-up was 1.0 months.

### Time to Event Endpoints

#### *Reviewer's Comments:*

*Analyses of time to progression, time to treatment failure, time to accelerated phase or blast crisis and overall survival were not done as they cannot be interpreted in a single-arm study.*

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### Subgroup Analysis

CML-CP: There was no difference in major cytogenetic response rate between patients aged < 65 years and those ≥ 65 years. Female patients had a similar response rate (47/92, 51.1%) to male patients (45/93, 48.9%). Most of the responders were of Caucasian race (85/92, 92%).

### Mutation Analysis

Baseline mutations were present in 52 (18.6%) patients. The various mutations present were D276G, E255K, E255V, E279K, E355A, E355G, E459K, F311L, F317L, F359V, F486S, G250E, H396R, L248V, L370P, L387M, M244V, M351T, S438C, T315I, Y253H, Y315I.

Fifteen out of the 52 patients (28.8%) had a major cytogenetic response. One patient had two baseline mutations. There were 10 patients who achieved a complete cytogenetic response and five patients achieved a partial cytogenetic response. There was no response in the patient with a T315I mutation.

### CML-AP

#### Primary Efficacy Analysis: Confirmed Hematologic Response

#### 120-Day Efficacy Update

The primary efficacy analysis was performed based on the primary 64 CML-AP and 41 additional patients who had either completed 4 months of treatment or discontinued the study. The major hematologic response (MHR) which included complete hematologic response and no evidence of leukemia?marrow response (CHR + NEL/MR) was 23.8% and the overall hematologic response (OHR) which included complete hematologic response, no evidence of leukemia and return to chronic phase (CHR + NEL/MR + RTC) was 37.1%.

**Table 28 Confirmed Hematologic Response CML-AP (Reviewer's Table)**

Confirmed Hematologic Response	Applicant Analyses <sup>a</sup>		FDA Adjudicated Analyses <sup>b</sup>	
	Additional Patients N=41 (%)	Primary and Additional Patients N=96 (%)	Additional Patients N=41 (%)	Primary and Additional Patients N=105 (%)
Overall Hematologic Response	9 (22.0)	43 (44.8)	7 (17.1)	27 (26%)
95% CI	10.6, 37.6	34.6, 55.3	7.2, 32.1	27.9, 47.1
Complete hematologic response	3	18 (18.8)	4 (9.8)	19 (18)
No evidence of leukemia	2	9 (9.4)	1 (2.4)	8 (7.6)
Return to chronic phase	4	16 (16.7)	2 (4.9)	14 (13.3)

<b>Major Hematologic Response</b>	5 (12.2)	27 (28.2)	5 (12.2)	25 (23.8)
95% CI	4.1, 26.2	19.4, 38.2	4.1, 26.2	16.0, 33.1
Complete hematologic response	3	18 (18.8)	4 (9.8)	17 (16.2)
No evidence of leukemia	2	9 (9.4)	1 (2.4)	8 (7.6)

<sup>a</sup> based on all ITT patients irrespective of protocol violations

<sup>b</sup> based on patients with no protocol violations

*Reviewer Comment : After further clarification from the sponsor, patient 0305\_006 with CML-AP was accepted by FDA as having a CHR and patient 0502\_03003 was accepted as having NEL. Therefore, the estimate of the hematologic response rate for AP patients was revised to 26% (27 / 105) (18% CHR + 8% NEL). The reviewer does not recommend inclusion of RTC in the hematologic response endpoint.*

### Duration of Confirmed Hematologic Response

Duration of confirmed responses were calculated for the the 26 patients with a major hematologic response (MHR) and the 39 patients with overall hematologic response (OHR). Median duration was not reached.

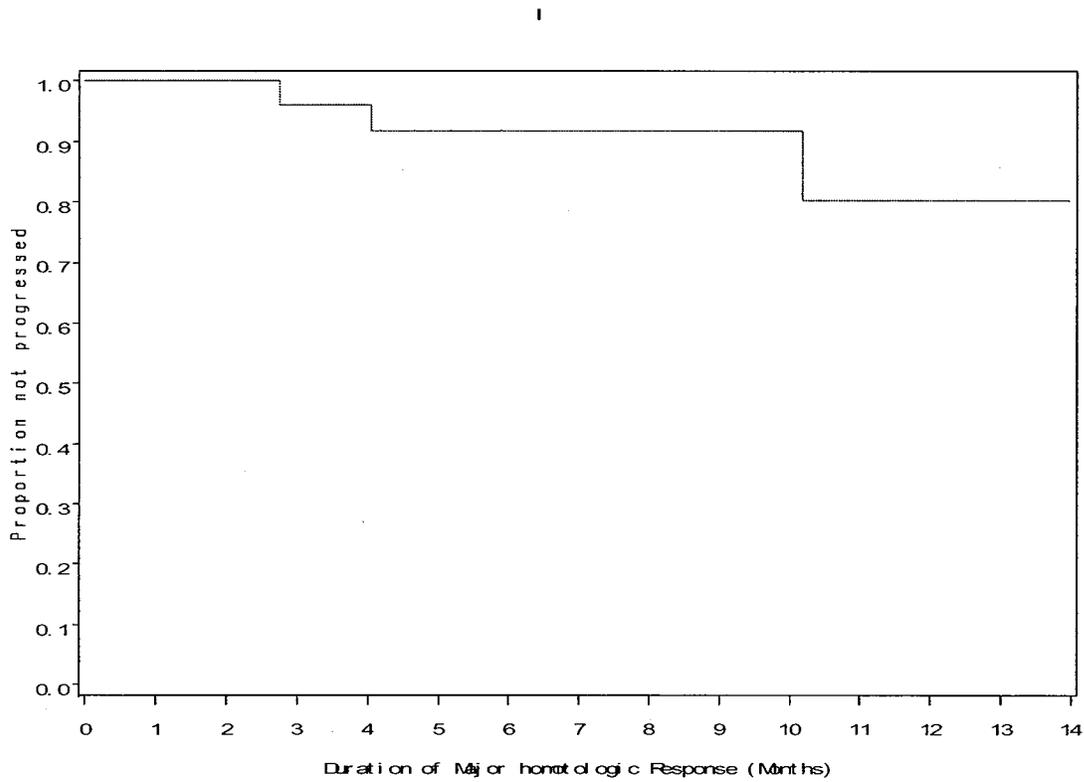
**Table 29 Duration Confirmed Hematologic Response CML-AP (Reviewer's Table)**

Duration (months)	FDA adjudicated OHR N=105	FDA adjudicated MHR N=105
Number of Responders	39 (100%)	26(100%)
Number censored	29 (74.4%)	23 (88.5%)
Median w 95% CI	0.95(0.03,3.94)	3.28(0.03,*)
25 percentile w 95% CI	4.86( (4.04, *)	* (10.18*)
50 percentile w 95% CI	*( 10.18)	*
75 percentile w 95% CI	*	*

The Kaplan-Meier curve for the duration of confirmed major hematologic response is shown below. The median duration of response has not been reached. The longest duration of MHR observed was 14 months.

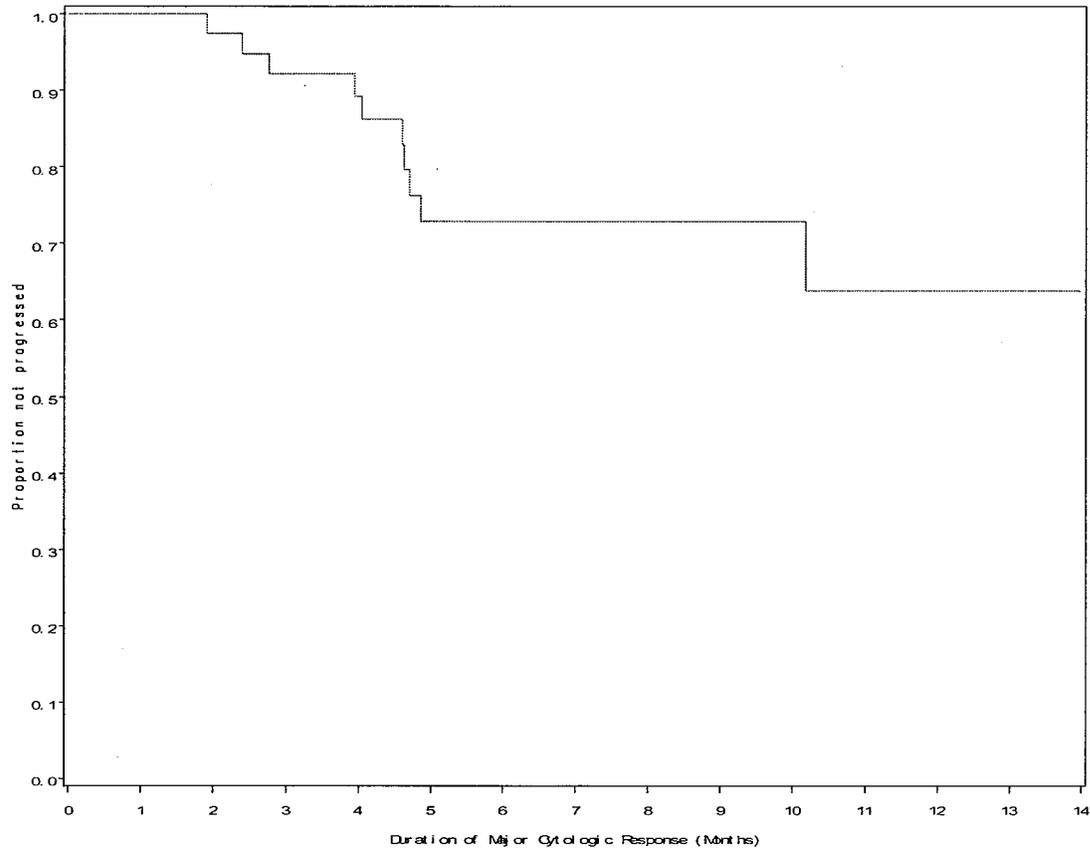


**Figure 3 Duration of MHR CML-AP K-M Curve (Reviewer's Figure)**



The Kaplan-Meier curve for the duration of confirmed overall hematologic response is shown below. The number of patients who maintained a OHR response  $\geq 3$  months was 33.3%; the number of patients who maintained OHR response  $\geq 6$  months was 18.1% and the number of patients who maintained OHR response  $\geq 12$  months was 4.8 %. The longest duration of OHR was 14 months.

**Figure 4 Duration of OHR for CML-AP patients K-M Curve (Reviewer's Figure)**



### **Time to confirmed major hematologic response**

Time to confirmed major hematologic response for the 26 responders was 1.0 month.

### **Loss of complete hematologic response**

Out of 18 patients in CHR in the primary and additional total 105 CML-AP patients, there was no loss of CHR in 15 patients of the 27 patients who achieved a HR in the study. One patient had a return to chronic phase, two patients had a loss of CHR before the cut-off date.

### **Cytogenetic Response**

#### **120-Day Efficacy Update**

The FDA reviewer analyzed the CML-AP patients for a cytogenetic response based on the same criteria used for the analysis of MCyR in CML-CP patients. This included baseline FISH not considered as acceptable baseline analysis, responses based on FISH considered as non-responders and patients whose baseline bone marrow cytogenetic analysis showed a partial response were classified as having no response if they remained in the partial response category.

An unconfirmed MCyR was seen in 16.2% patients and confirmed MCyR in 4.1% patients. A confirmed complete cytogenetic response was seen in 3 patients (2.9%).

**Table 30 Cytogenetic Response CML-AP Patients (Reviewer's Table)**

	Applicant Analysis CyR N=96 (%)	FDA adjudicated Analysis CyR N=105 (%) but only 81 evaluable*	
	Unconfirmed	Unconfirmed	Confirmed
Major Cytogenetic Response (Complete + Partial)	29 (30.2)	17 (16.2)	5 (4.1)
95% CI	21.3, 40.4	9.7, 24.7	1.6, 10.8
Complete	15 (15.6)	9 (8.6)	3 (2.9)
Partial	14 (14.6)	8 (6.7)	2 (1.9)
Minor	12 (12.5)	3 (2.9)	
Minimal	20 (20.8)	13 (12.4)	
None	16 (16.7)	21 (20.0)	

### Duration of Major Cytogenetic Response

The median duration was not reached. The longest duration seen was 13.6 months.

**Table 31 Duration Major Cytogenetic Responders CML-AP (Reviewer's Table)**

Duration (months)	FDA adjudicated unconfirmed MCyR N=105	FDA adjudicated confirmed MCyR N=105
Number of Responders	17	5
Number censored	14	5
Median w 95% CI	*(14.37,*)	*
25 percentile w 95% CI	4.37 (2.17,*)	*
75 percentile w 95% CI	*	*

### **Time to major cytogenetic response/complete cytogenetic response**

Time to major cytogenetic response/complete cytogenetic responders for the 17/9 responders was 2.8 months.

### **Loss of major cytogenetic response (MCyR)**

Out of the 17 patients who had an MCyR, two patients had a loss of MCyR by the cut-off date.

### **Time to Event Endpoints**

#### *Reviewer's Comments:*

*Analyses of time to progression, time to treatment failure, and overall survival were not done as they cannot be assessed in a single-arm study.*

### **Subgroup Analysis**

CML-AP: The major hematologic response was higher in patients < 65 years of age (22/72, 31 %) than in patients ≥ 65 years (5/33, 15 %). The response rate was slightly higher in males (14/26, 54 %) than females (12/26, 46 %).

### **Mutation Analysis**

Baseline mutations were present in 26 (24.8%) patients. The various mutations present were D276G, E255K, E279K, E450G, E459K, F317I, F317L, F359V, G250E, H396R, M244V, M351T, Q252H, T277S, T315I, and Y253H.

Out of the 26 patients, 12 (46.2%) patients has an overall hematologic response as shown below. There were three patients with 2 mutations at baseline. Three patients achieved a CHR, 3 patients achieved no evidence of leukemia and 6 patients achieved return to chronic phase responses.

### **Population who received prior TKIs other than imatinib**

#### **CML-CP and CML-AP**

The applicant submitted supportive studies contributing data to the nilotinib efficacy update in CML-CP and CML-AP patients who received prior TKIs other than imatinib. These were patients in Study 2101, Arm 3, Group B — and Arm 4, Group B — The 120-day efficacy update had 22 patients in the CML-CP group and 11 patients in the CML-AP group. The

applicant reported a 50% major cytogenetic response rate in the CML-CP group and 9.1 % major hematologic response rate in CML-AP group.

*Reviewer's Comments:*

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**Population who Received Prior Dasatinib and Imatinib**

The applicant also submitted data in CML-CP and CML-AP patients who had received dasatinib after imatinib. This was based on a follow up of 4 months.

**CML-CP**

The applicant's table of responses is shown below.

**Table 32 Best Cytogenetic Response CML-CP Patients with 4 months follow-up (Applicant's Table)**

	<b>Baseline CHR</b> N = 5 n (%)	<b>No Baseline CHR</b> N = 17 n (%)	<b>Total</b> N = 22 n (%)
<b>Cytogenetic responses</b>			
<b>MCyR*</b>	2 (40)	5 (29)	7 (32)
CCyR	1 (20)	2 (12)	3 (14)
PCyR	1 (20)	3 (18)	4 (18)

The applicant submitted the best cytogenetic response to nilotinib in the 7/22 patients with CML-CP.

There were 22 patients in the CML-CP group. Three of the patients were diagnosed based on baseline FISH and two patients were considered responders based on FISH analysis. These three patients were excluded. One patient had baseline PCyR and was considered eligible for a CCyR, thus the PCyR response could not be considered. One patient had a CCyR at baseline and could not be considered for a response. Thus there were two responses that the FDA agreed with, one a CCyR and the other a PCyR. The applicant's and the FDA reviewer's adjudicated data is shown in the table below.

**Table 33 Best Cytogenetic Response in CML-CP (Reviewer's Table)**

Cytogenetic Responses	Applicant's Response N=22 (%)	FDA Adjudicated Response N=19 (%)
MCyR	7 (32)	2 (10.5)
CCyR	3 (14)	1 (5.3)
PCyR	4 (18)	1 (5.3)

### CML-AP

There were 13 patients in the CML-AP group. There were six patients described. FDA agreed with all six responses.

**Table 34 Best Hematologic Response in CML-AP (Applicant's Table)**

Hematologic Response	Applicant's Response N=13 (%)
Overall Hematologic Response	6 (46)
CHR	0
NEL	3 (23)
RTC	3 (23)
Major Hematologic Response (CHR + NEL)	3 (23)

*Reviewer's Comments:*

*There were no raw datasets submitted for these patients. The reviewer adjudication is based on the derived datasets. The number of patients in these two groups are too small for interpretation.*

#### 6.1.5 Clinical Microbiology

Not applicable

#### 6.1.6 Efficacy Conclusions

Evidence of nilotinib efficacy is based on the results of a single Phase 2 study with two populations studied, CML-CP and CML-AP. The primary efficacy endpoint in CP-CML population was major cytogenetic response (MCyR), defined as elimination or diminution to less than 35% of Ph<sup>+</sup> hematopoietic cells. The primary efficacy endpoint in CML-AP was overall hematologic response which included complete hematologic response (CHR) or no evidence of leukemia (NEL) and return to chronic phase. CHR and NEL (a major hematologic response)

were considered as surrogates reasonably likely to predict clinical benefit for accelerated approval.

CML-CP: A total of 92 of 232 evaluable patients (40%) achieved an unconfirmed MCyR (95% CI: 33, 46). This was comprised of a complete response rate of 28% and a partial response rate of 12%. Fifty-nine percent of CML-CP patients with a major cytogenetic response had a duration of response of at least 6 months.

CML-AP: A total of 27 of 105 evaluable patients (26%) achieved a hematologic response rate (95% CI:18,35). This included a complete hematologic response in 18% and no evidence of leukemia/marrow response in 8% of patients.

#### Secondary efficacy endpoints

CML-CP: Complete hematologic response was observed in 92 patients (50%) of the 185 patients in the primary and additional population who were without CHR at baseline and therefore assessable for CHR.

CML-AP: An unconfirmed MCyR was seen in 20% of evaluable patients.

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#### Subgroup Analyses:

In the single study, approximately 30% of patients were 65 or over.

CML-CP: There was no difference in major cytogenetic response rate between patients aged < 65 years and those  $\geq$  65 years. Female patients had a similar response rate (47/92, 51.1%) to male patients (45/93, 48.9%). Most of the responders were of Caucasian race (85/92, 92%).

CML-AP: The major hematologic response was higher in patients < 65 years of age (22/72, 31%) than in patients  $\geq$  65 years (5/33, 15%). The response rate was slightly higher in males (14/26, 54%) than females (12/26, 46%).

#### Limitations of Data

Efficacy was based on a single clinical trial only with two groups of CML, CML-CP and CML-AP. There was no comparator arm because it was deemed that no effective control therapy was available.

The efficacy conclusions are based on interim data of ongoing studies. There were two cut-off dates for the primary and additional patient analyses. The number of additional patients were greater than the number in the primary analysis submitted in the initial NDA submission in the CML-CP population. All CML-CP patients had at least a 6-month follow-up and all CML-AP patients had at least a 4-month follow-up. These follow-up periods were sufficient for evaluation of response rates, but not for duration of responses. The median duration of response had not been reached in both the CML-CP and CML-AP populations.

The efficacy endpoints were not assessed by an independent review team which could be subject to bias.

The protocol specified the use of FISH analysis when bone marrow cytogenetics were not available. FISH is not a validated test and only bone marrow cytogenetics were deemed assessable for major cytogenetic response for CML-CP population in this submission for accelerated approval. Response rates by bone marrow cytogenetics were considered a surrogate endpoint reasonable likely to predict clinical effectiveness for accelerated approval.

The protocol specified primary efficacy endpoint in CML-AP was overall hematologic response which included complete hematologic response (CHR) or no evidence of leukemia (NEL) and return to chronic phase. Only CHR and NEL (a major hematologic response) were considered as surrogates reasonably likely to predict clinical effectiveness for accelerated approval.

#### Efficacy Conclusions

The efficacy data demonstrate that nilotinib treatment results in cytogenetic and hematologic responses in patients with CML-CP and CML-AP who are imatinib-resistant or intolerant on imatinib. Most responses occurred within 3 months of initiation of therapy. Responses that lasted for approximately 14 months were observed. The number of patients in the population who received prior dasatinib and imatinib were too small for interpretation.

The trial was conducted per protocol except for certain eligibility criteria. The trial appears to have been well conducted. The largest accruing groups and those with the most responses were not found to have potentially confounding deficiencies on FDA site inspection.

The results of the trial provide evidence that nilotinib is effective as a single agent in CML-CP and CML-AP groups who are imatinib-resistant or intolerant to prior imatinib. The primary analysis is conservative, since patients who were not assessable for response were counted as non-responders.

Cytogenetic and hematologic responses in imatinib resistant or intolerant CML-CP and CML-AP patients respectively, who have limited treatment options, are reasonably likely to predict clinical benefit and therefore support accelerated approval.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

Adverse events (AEs) were coded using the MedDRA dictionary that provided the system organ class and preferred term information. The applicant was queried on the version of MedDRA used to code adverse events. They stated that the MedDRA version used at time of submission was 9.0. AEs were summarized by presenting the number and percentage of patients having an adverse event in each system organ class, and having an adverse event with a particular preferred term within a system organ class. AEs were summarized only when they started on or after the start of the nilotinib, and within 28 days of discontinuation of the nilotinib (not study discontinuation). AEs were summarized and listed by NCI CTC grades for each AE using version 3.0. AEs that were suspected to be nilotinib related were summarized separately. Except cardiac enzymes and urinalysis data, none of the lab results were documented on the annotated CRF, but captured electronically. The WHO\_DRL dictionary was used to code concomitant medications.

The results from the two arms of the single, currently-ongoing, Phase 1/2 open-label study, Study 2101, form the foundation of the safety analysis with use of the remainder of the safety database for assessment of serious and rare AEs. One arm included 282 patients in the primary population and 318 patients in the primary and additional population with imatinib-resistant or –intolerant CML-CP without prior tyrosine kinase inhibitors other than imatinib (Arm 4, Group A). These latter patients received the first dose of nilotinib on or before August 4, 2006 and the cut-off date for the data was September 4, 2006. The second arm included 89 patients in the primary population and 120 patients in the primary and additional patients with imatinib-resistant or –intolerant CML-AP without prior tyrosine kinase inhibitors other than imatinib (Arm 3, Group A). These latter patients received the first dose of nilotinib on or before August 23, 2006 and the cut-off date for the data was September 23, 2006. The two arms were not pooled for the safety analysis because of the different patient populations, and lack of appropriate controls, particularly given the high background rate of adverse events in patients with imatinib-resistant or –intolerant CML-CP and CML-AP.

#### 7.1.1 Deaths/ Sudden Deaths

##### CML-CP

The applicant reported three deaths in this study. Only deaths on or within 28 days of study were reported. Two of these 3 patients has sudden death.

Patient 0505\_04001 died suddenly on study day 20. An autopsy revealed secondary calcific coronary atherosclerosis, with severe 1 vessel disease with grade 4 stenosis in LAD, grade 3 in the left circumflex and right coronary artery and grade 2 in left main artery.

Patient 0304\_04010 died suddenly on study day 265. An autopsy revealed evidence of an acute myocardial infarction with 50 to 90% occlusion in two coronary arteries and evidence of an old myocardial infarction. In addition, evidence of left ventricular rupture and large pericardial effusion was observed.

Patient 0305\_04006 was a 62 year old male who on day 28 was diagnosed with Grade 4 renal failure and sepsis. The patient further deteriorated, developing Grade 4 hepatic failure and died on study day 30.

An additional narrative was written for Patient 0702\_04007 whose death, due to gastrointestinal ulcer perforation followed by peritonitis and multiorgan failure, occurred 9 days after nilotinib discontinuation. This patient died 4 days after data cut-off and was therefore not included in this data.

**Table 35 Overview of Deaths CML-CP (Applicant's Table)**

Site Patient No. Age/sex/race	Total daily dose	Adverse Event	Study day of death	Study drug relationship
0304 04010 73/M/Ca	800 mg	Myocardial infarction	265	Not suspected
0350 04006 62/M/Ca	800 mg	Multi-organ failure	30	Suspected
0505 04001 69/M/Ca	800 mg / 400 mg	Arteriosclerosis coronary artery	20	Suspected

Ca = Caucasian

Source: PT-Listing 14.3.2-1.1

### CML-AP

The applicant reported seven deaths in this study. Three deaths were reported as suspected to be related to nilotinib. Two of the patients had thrombocytopenia, one leading to intracerebral bleeding. One patient developed congestive heart failure on 600 mg bid dose of nilotinib. One patient had a sudden death.

Patient 0302\_03002 was a 60 year old Caucasian male with imatinib resistant CML. At baseline this patient had Grade 4 thrombocytopenia. On Day 4 the patient was hospitalized for Grade 3 aphasia, Grade 3 disorientation and Grade 3 disturbance in attention. The patient died on Day 6 and death was preceded by an adverse event of intracerebral bleeding.

Patient 0308\_03001 was a 64 year old Caucasian female with imatinib resistant CML and past medical history of obesity, hypertension and edema. On study day 141 the patient experienced Grade 4 thrombocytopenia leading to interruption of nilotinib therapy which resumed on Day 151. On study day 189, the patient was hospitalized with Grade 4 pneumonia, thrombocytopenia and overall physical deterioration leading to permanent discontinuation of drug on Day 191. The patient's condition deteriorated and death occurred on Day 209.

Patient 0350\_03004 was a 77 year old Caucasian male with imatinib resistant CML who was dose escalated to 600 mg b.i.d. of nilotinib and died on study day 122 and whose death was preceded by an adverse event of congestive heart failure. This patient had a medical history of hypertension and first degree AV block on ECG. Baseline LVEF was 60%. On Day 117 patient was diagnosed with pneumonia, anemia and pulmonary edema. The patient subsequently was diagnosed with heart failure and died despite with diuretics, RBC transfusions, oxygen and broad spectrum antibiotics.

The following four deaths were reported as not suspected to study drug.

Patient 501\_3002 was a 63 year old Caucasian male with imatinib resistant CML with a past medical history of smoking and atrial fibrillation and left anterior hemiblock. At study entry the patient had Grade 2 anemia and Grade 4 thrombocytopenia, leukocytosis and progressive weakness. On study day 6 the patient was hospitalized with febrile neutropenia, hypotension, chest pain, dyspnea and syncopal episode. On day 7 the patient was in atrial fibrillation requiring treatment with amiodarone, digoxin and nitrates. Nilotinib was discontinued on day 7 and the patient was discharged from hospital on day 20. The patient died 21 days after discontinuation of nilotinib.

Patient 0501\_3008 was a 76 year old Caucasian female with imatinib resistant CML. The patient died on study day 98 and death was preceded by an adverse event of sepsis. On study day 78, Grade 4 sepsis and Grade 3 nocardia infection was diagnosed. Nilotinib was discontinued on day 79, 20 days prior to death.

Patient 0516\_03001 was a 75 year old caucasian male with imatinib resistant CML. Approximately 9 months after initiation of nilotinib, the patient experienced disease progression. The patient died 13 days after the determination of disease progression.

Patient 0901\_03001 was a 50 year old caucasian female with imatinib resistant CML and a past medical history of gastrointestinal hemorrhage. On Day 29 the patient's dose was reduced to 400 mg q.d. due to Grade 4 neutropenia. On Day 86 the patient was hospitalized for Grade 4 leukocytosis and decreased performance status leading to permanent discontinuation of nilotinib medication. Ten days after discontinuation of nilotinib, the patient developed grade 4 multi-organ failure and died the same day.

**Table 36 Overview of Deaths CML-AP (Applicant's Table)**

Site Patient No. Age/sex/race	Total daily dose	Adverse Event	Study day of death	Study drug relationship
0302 03002 60/M/Ca	800 mg	Progressive CML, complicated by intracerebral bleeding	6	Suspected
0308 03001 64/F/Ca	800 mg	Disease progression	209	Suspected
0901 03001 50/F/Ca	800/400 mg	Study indication	95	Not suspected
0350 03004 77/M/Ca	800/1200 mg	Cardiac failure	122	Suspected
0501 03002 63/M/Ca	800 mg	Study indication	27	Not suspected
0501 03008 76/F/Ca	800 mg	Sepsis	98	Not suspected
0516 03001 74/M/Ca	800 mg	Study indication	284	Not suspected

Source: Post-text listing 14.3.2-1.1

*Reviewer's Comments:*

1. Patient 0516\_03001 and Patient 0501\_3008 had severe neutropenia which could have been related to study drug.

**120-Day Safety Update**

The applicant recorded three additional deaths from the previous 10 deaths in CML-CP and CML-AP patients in Table 4-18 in the 120-day safety update study report. These were deaths reported while patients were on study or within 30 days after drug was discontinued. Thus, there were a total of 13 deaths in the two populations.

**Table 37 Overview of Deaths CML-CP and CML-AP 120-Day Update (Reviewer's Table)**

Patient ID	Age	Disease Phase	Day of Death	Cause of death in dataset (S=suspected)	FDA Comments
0304_04010	73	CP	265	MI	Sudden death. Autopsy acute MI, ventricular rupture, large pericardial effusion. h/o MI
0350_04006	62	CP	30	Multi-organ failure (S)	G 4 renal failure/sepsis; G 4 hepatic failure day 30 (S)
0505_04001	69	CP	20	Arteriosclerosis	Sudden death. Autopsy coronary

				coronary artery (S)	atherosclerosis
0302_03002	60	AP	6	Intracerebral bleed (S)	Thrombocytopenia followed by intracerebral bleed (S)
0308_03001	64	AP	209	Progression (S)	G 4 Thrombocytopenia, G 4 pneumonia day 189; drug discontinued day 191 (S)
0901_03001	50	AP	95	Study indication	G 4 neutropenia day 29; G 4 leukocytosis day 86; multi-organ failure day 95
0350_03004	77	AP	122	Cardiac failure (S)	h/o hypertension, first degree AV heart block , LVEF 60%; pulmonary edema, cardiac failure day 117 (S)
0501_03002	63	AP	27	Study indication	h/o A fibrillation; syncope on day 6, A. fibrillation on day 7; drug discontinued day 8; found dead at home day 27 (S)
0501_03008	78	AP	98	sepsis	G 4 sepsis/nocardia infection on day 78; died day 98 (S)
0516_03001	74	AP	284	Study indication	progression
0702_04007	51	CP	244	sepsis	G4 Perforated duodenal ulcer on day 226, drug discontinued day 235, G 3 peritonitis day 244 (S)
0807_03002	70	AP	5	Lung infection	Grade 3 pneumonitis and grade 3 lung infection; white counts not provided
0211_03001	74	AP	126	Metastatic melanoma	Not suspected

Source: Dataset A\_DTH.xpt; death narratives

### **Sudden Deaths**

In Feb3, 2006, Novartis informed the Agency regarding six (6) sudden deaths that had occurred in the AMN107 trial. They stated that two of the deaths appeared to be unrelated to AMN107 after autopsies were conducted. However, the cause of death was uncertain in four of the cases. Novartis included further measures in the exclusion criteria to exclude prior cardiac disorders, informed the investigators and proposed a dedicated QT study which was subsequently conducted in healthy volunteers.

In the updated datasets, there were a total of ten sudden deaths. There were six sudden deaths reported in the safety population and four sudden deaths reported from the expanded access

protocol or single patient compassionate use protocols. Patients 0304\_04010 and 0505\_04001 were from the safety population defined in the indication (318 CML-CP and 120 CML-AP patients).

The table below shows the details of the cause of death for the six sudden deaths in the safety population.

**Table 38 Overview of Sudden Deaths in Study 2101 (Reviewer's Table)**

<b>Patient ID/ Center</b>	<b>Age/ Gender</b>	<b>Study/ Dose</b>	<b>Day of Death</b>	<b>Details of Cause of Death</b>
0303_01001 Germany	75/F	Phase 2 Ph+ ALL 400 bid	7	Hypokalemia day -1; QTc increased from baseline 431.5 to 499.5 msec and 68 msec change day 2, Day 7 electrolytes unknown. Cause of death: sudden cardiac arrest; no autopsy. Sponsor suspected causality.
0505_04001 USA	69/M	Phase 2 CML CP 400 bid	20	h/o CAD. Found unresponsive at home on day 20. Autopsy: coronary atherosclerosis with one vessel disease with multiple stenoses, contributing pulmonary hypertension, RVH, arterial vasculopathy. Cause of death: coronary artery stenosis. Investigator suspected relationship of sudden death to study drug.
0501_00103 USA	52/M	Phase 1 CML CP 400 bid	194	Hypokalemia day 183. Unresponsive on day 194, ventricular fibrillation; no obvious concomitant medications; no h/o cardiac disease; investigator could not exclude QT prolongation.
0304_05001 Germany	66/M	Phase 2 CEL/HES 400 bid	15	QTc baseline 446.3 increased to 456.3 on day 2; pancytopenia day 11 suspected related to study drug and hospitalized; verapamil treatment (CYP 3A4 inhibitor). Day 15 sudden death; cardiac arrest/asystole. Autopsy: aseptic endocarditis, old MI, pleural and pericardial effusion. Investigator did not suspect relationship to study drug based on autopsy.
0502_00122	31/M	Phase 1	177	Day 177, found dead at home. Autopsy:

USA		CML AP 400 bid		“high” levels of methadone in blood. Cause of death: methadone overdose. (Methadone prolongs QT interval and/or induces TdP). Investigator did not suspect a relationship to study drug.
0304_04010 Germany	73/M	Phase 2 CML CP 400 bid	265	Day 265 found dead by family. Last ECG day 246 normal. Investigator suspected sudden death due to cardiac arrest. Autopsy: unknown CAD with old MI, coronary artery occlusion and large pericardial effusion. Investigator did not suspect a relationship with study drug.

Source: Narratives

The table below shows the details of the four sudden deaths in the expanded access protocol or with single patient compassionate use.

**Table 39 Overview of Sudden Deaths in Expanded Access Protocol or Single Patient Compassionate Use**

Patient ID/ Center	Age/ Gender	CML Phase/ Dose	Day of Death	Details of Cause of Death
0514_00015 USA	65/F	AP in CHR 800 bid	5	Baseline ECG showed old LBBB; echo normal; no h/o cardiac disease. Died suddenly day 5. Fluconazole treatment, no ECG at time of death, investigator noted cause as Grade 5 arrhythmia (fluconazole CYP 3A4 inhibitor). Suspected causality.
503-9	49/M	CP	60	h/o CAD, found dead at home; recent ECG, electrolytes unremarkable; no obvious concomitant medications; investigator suspected sudden death to be related to study drug.
106-1 Canada	46/F	BC 800 qd	43	Study drug stopped 4 days prior. Chest pain and cardio-respiratory arrest on day 43. No cardiac history; no obvious concomitant medications. Investigator stated MI and suspected causality.
307-1 Germany	78/F	CP in remission	150	Day 150 found dead in bed; QTc 456 2 months prior; treatment with

		800 qd		moxifloxacin for 1 week prior to death for upper respiratory infection (moxifloxacin prolongs QT).
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The actual mode of death is unclear for these patients and whether QT prolongation due to nilotinib played a role cannot be answered definitively. The relative early occurrence of these events suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence. There are no randomized controlled trials for comparison.

Nonetheless in three of the cases the timing and circumstances suggest that nilotinib administration may have been related to death. These three are:

- 0303/01001, an older female left ventricular dysfunction and hypokalemia, whose demonstrated prolonged QTc on the second day of nilotinib therapy and then died on day 7, which is approximately the time of C<sub>max</sub> was reached.
- 0514/00015, an older female with abnormal baseline ECG co-administered fluconazole (a QT prolonger as well as a CYP3A4 inhibitor) who died on day 5, which is approximately the time the new C<sub>max</sub> was attained.
- 307-1, an older female who was co-administered moxifloxacin (a QT-prolonger), and then died eight days later.

These three cases suggest a concentration dependent relation of nilotinib to sudden death.

*Reviewer's Comments:*

*The actual mode of death is uncertain for these patients and whether QT prolongation due to nilotinib played a role cannot be answered definitively. The relative early occurrence of some of these events suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence. Several patients were on concomitant medications which either prolonged QT interval or were associated with TdP or were CYP inhibitors.*

*The label should include a black boxed warning including the sudden deaths and relation to QT prolongation as well as caution against using concomitant medications which prolong QT interval or are CYP inhibitors. Testing ECGs and electrolytes at baseline and periodically and taking nilotinib as recommended with the food interval is recommended and should be included in the boxed warning.*

### 7.1.2 Other Serious Adverse Events

Deaths including sudden deaths have been discussed in the previous section.

### Serious Adverse Reactions

The applicant coded the serious AEs bases on the investigator's assessment.

In the CML-CP patients, the common Grade 3 and 4 serious AEs (>1%) identified were thrombocytopenia, neutropenia, angina pectoris and myocardial infarction.

In the CML-AP patients, the commonest Grade 3 and 4 serious AEs (>1%) identified were thrombocytopenia, neutropenia, leukopenia, abdominal pain, pyrexia, asthenia, pneumonia, elevated lipase, intracranial hemorrhage, dyspnea and respiratory failure.

The reviewer analyzed the Grade 3 and 4 AEs which provides a meaningful assessment of serious AEs in the cancer population and AEs leading to hospitalizations.

### **120-Day Safety Update**

#### **CML-CP**

Grade 3 and 4 AEs for the CML-CP population is shown in the table and chart below.

The commonest Grade 3 and 4 AEs reported in the CML-CP patients were thrombocytopenia/platelet count decreased (24.2%), neutropenia/neutrophil count decreased (17%), anemia (6.9%), elevated lipase (6.9%), elevated AST/ALT (4.4%), hyperbilirubinemia/bilirubin increased (3.2%), diarrhea (2.8%), headache (2.8%), arthralgia (2.2%), angina pectoris (1.9%), hyperglycemia (1.6%), rash (1.6%), myalgia (1.6%), myocardial infarction (1.3%), febrile neutropenia (1.3%), abdominal pain (1.3%), nausea (1.3%), fatigue (1.3%), pyrexia (1.3%), hyponatremia (1.3%), dyspnea (1.3%), extremity pain (1.3%).

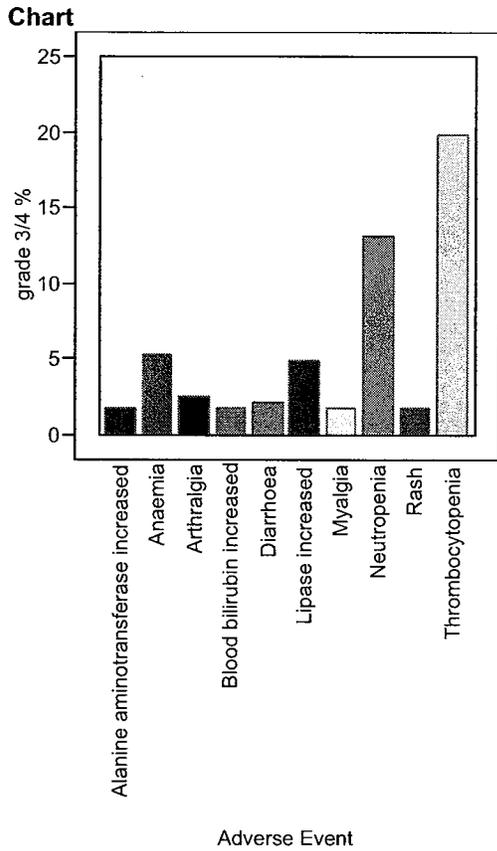
**Table 40 Grade 3/4 Adverse Reactions > 1% CML-CP (N=318) (Reviewer's table)**

Adverse Event	Grade 3	Grade 3%	Grade 4	Grade 4%	Grade s 3/4	Grades 3/4 %
<b>Blood and lymphatic system disorders</b>						
Thrombocytopenia	31	9.7	39	10.7	70	22.0
Neutropenia	27	8.5	22	5.3	49	15.4
Anaemia	18	5.7	4	1.3	22	6.9
Leukopenia	8	2.5	0	1.3	8	2.5
Thrombocythaemia	6	1.9	0	0.0	6	1.9
Febrile neutropenia	4	1.3	0	0.0	4	1.3
<b>Cardiac disorders</b>						
Angina pectoris	6	1.9	0	0.3	6	1.9
Myocardial infarction	0	0.0	4	0.3	4	1.3
<b>Gastrointestinal disorders</b>						
Diarrhoea	9	2.8	0	0.3	9	2.8
Abdominal pain	4	1.3	0	0.0	4	1.3
Nausea	3	0.9	1	0.0	4	1.3
<b>General disorders and administration site conditions</b>						

Fatigue	4	1.3	0	0.0	4	1.3
Pyrexia	4	1.3	0	0.0	4	1.3
<b>Hepatobiliary disorders</b>						
Hyperbilirubinaemia	5	1.6	0	0.0	5	1.6
<b>Investigations</b>						
Lipase increased	18	5.7	4	0.9	22	6.9
Alanine aminotransferase increased	7	2.2	0	0.0	7	2.2
Platelet count decreased	3	0.9	4	0.3	7	2.2
Blood amylase increased	5	1.6	0	0.0	5	1.6
Blood bilirubin increased	5	1.6	0	0.0	5	1.6
Blood creatine phosphokinase increased	3	0.9	1	0.0	4	1.3
Blood glucose increased	3	0.9	1	0.0	4	1.3
Neutrophil count decreased	2	0.6	2	0.6	4	1.3
<b>Metabolism and nutrition disorders</b>						
Hyperglycaemia	5	1.6	0	0.0	5	1.6
Hyponatraemia	3	0.9	1	0.0	4	1.3
<b>Musculoskeletal and connective tissue disorders</b>						
Arthralgia	6	1.9	1	0.0	7	2.2
Myalgia	5	1.6	0	0.0	5	1.6
Pain in extremity	4	1.3	0	0.0	4	1.3
<b>Nervous system disorders</b>						
Headache	8	2.5	1	0.0	9	2.8
<b>Respiratory, thoracic and mediastinal disorders</b>						
Dyspnoea	4	1.3	0	0.0	4	1.3
<b>Skin and subcutaneous tissue disorders</b>						
Rash	5	1.6	0	0.0	5	1.6

Source: A\_AEV.xpt

**Figure 5 Grade 3/4 Adverse Events CML-CP (Reviewer's Chart)**



AEs leading to hospitalizations in at least two patients included thrombocytopenia, myocardial infarction, angina pectoris, malaise, pyrexia, arthralgia, febrile neutropenia, neutropenia, pericardial effusion, abdominal pain, diarrhea, pancreatitis, vomiting, cholelithiasis, bone pain, extremity pain, vasovagal syncope and pleurisy.

**Table 41 Adverse Events Leading to Hospitalizations in at least 2 Patients CML-CP N=282 (Reviewer's Table)**

Adverse Event	All grades	All grades %	Grades 3/4	Grades 3/4%
Thrombocytopenia	4	1.4	4	0.5
Myocardial infarction	4	1.4	4	0.5
Angina pectoris	3	1.1	3	0.4
Malaise	3	1.1	0	0.4
Pyrexia	3	1.1	1	0.4
Arthralgia	3	1.1	2	0.4
Febrile neutropenia	2	0.7	2	0.3
Neutropenia	2	0.7	2	0.3

Pericardial effusion	2	0.7	1	0.3
Pericarditis	2	0.7	2	0.3
Abdominal pain	2	0.7	2	0.3
Diarrhoea	2	0.7	2	0.3
Pancreatitis	2	0.7	0	0.3
Vomiting	2	0.7	1	0.3
Cholelithiasis	2	0.7	2	0.3
Bone pain	2	0.7	1	0.3
Pain in extremity	2	0.7	1	0.3
Syncope vasovagal	2	0.7	2	0.3
Pleurisy	2	0.7	2	0.3

Source: A\_AEV.xpt

### CML-AP

Grade 3 and 4 AEs for the CML-AP population is shown in the table and chart below.

The commonest Grade 3 and 4 AEs reported in the CML-AP patients were thrombocytopenia/platelet count decreased (36.7%), neutropenia/neutrophil count decreased (20%), anemia (15.8%), elevated lipase (9.2%), leukopenia (6.7%), hyperbilirubinemia/bilirubin increased (5%), febrile neutropenia (2.5%), abdominal pain (2.5%), dyspnea (2.5%), thrombocythemia (1.7%), angina pectoris (1.7%), diarrhea (1.7%), pyrexia (1.7%), headache (1.7%), extremity pain (1.7%).

**Table 42 Grade 3/4 Reactions > 1% CML-AP (N=120) (Reviewer's table)**

Adverse Event	Grade 3	Grade 3%	Grade 4	Grade 4%	Grades 3/4	Grade 3/4%
<b>Blood and lymphatic system disorders</b>						
Thrombocytopenia	7	5.8	34	28.3	41	34.2
Neutropenia	7	5.8	17	14.2	24	20.0
Anaemia	12	10.0	4	3.3	16	13.3
Leukopenia	4	3.3	4	3.3	8	6.7
Thrombocythaemia	2	1.7	0	0.0	2	1.7
Febrile neutropenia	3	2.5	0	0.0	3	2.5
<b>Cardiac disorders</b>						
Angina pectoris	1	0.8	1	0.8	2	1.7
<b>Gastrointestinal disorders</b>						
Diarrhoea	1	0.8	1	0.8	2	1.7
Abdominal pain	3	2.5	0	0.0	3	2.5
<b>General disorders and administration site conditions</b>						
Pyrexia	2	1.7	0	0.0	2	1.7