

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-068**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 22-068

SUPPL #

HFD # 150

Trade Name Tassigna

Generic Name Nilotinib

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known October 29, 2007

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**  
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:



Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

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Name of person completing form: Janet Jamison  
Title: Regulatory Project Manager  
Date: October 16, 2007

Name of Office/Division Director signing form: Robert Justice, M.D.  
Title: Director, Division of Drug Oncology Products, OODP, CDER

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

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Robert Justice  
10/25/2007 06:04:45 PM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-068 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: September 29, 2006 PDUFA Goal Date: July 29, 2007

HFD-150 \_\_\_\_\_ Trade and generic names/dosage form: Tasigna (nilotinib) Capsules

Applicant: Novartis Pharmaceuticals Corporation Therapeutic Class: 1 V S

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.  
 No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): \_\_\_\_\_

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to at least one prior therapy including Gleevec (imatinib).

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.  
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.  
 No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population  
 Disease/condition does not exist in children  
 Too few children with disease to study  
 There are safety concerns  
 Other: \_\_\_\_\_

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

NDA 22-068

Page 3

**This page was completed by:**

*{See appended electronic signature page}*

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**Christy Cottrell**  
**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH  
STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

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/s/

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Christy Cottrell  
12/20/2006 02:38:58 PM



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology

Date: July 12, 2007

To: Robert Justice, M.D., Director  
Division of Drug Oncology Products

Thru: Ellis Unger, M.D., Deputy Director  
Office of Surveillance and Epidemiology

From: **Nilotinib RiskMAP Review Team**  
Jeanine Best, MSN, RN, PNP, Patient Product Information Specialist, DSRCS  
Sam Chan, PharmD, MBA, Regulatory Health Project Manager, DSRCS  
Mary Dempsey, Risk Management Program Coordinator, OSE-IO  
Claudia Karwoski, PharmD, Team Leader Risk Management Team, OSE-IO  
Kim Pedersen, RPh, Safety Evaluator, DMETS  
Jennifer Steele, PharmD, Safety Evaluator, DDRE  
Joyce Weaver, PharmD, BCPS, Senior Drug Risk Management Analyst, OSE-IO  
Mary Willy, PhD, Senior Drug Risk Management Analyst, OSE-IO

Subject: Review of Proposed RiskMAP

Drug Name(s): Nilotinib (Tasigna) capsules

Application Type/Number: NDA: 22-068

Applicant/sponsor: Novartis Pharmaceuticals

OSE RCM #: 2007-915

Title OSE Safety Review

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## EXECUTIVE SUMMARY

This is a review of the Sponsor's Risk Minimization Action Plan (RiskMAP) for nilotinib (Tasigna), a tyrosine kinase inhibitor proposed for the treatment of Chronic Phase or Accelerated Phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to [REDACTED] prior therapy including imatinib. The Sponsor proposes an education-based RiskMAP, in addition to labeling, to minimize the risks of QTc prolongation, drug-drug interactions, and food effects (i.e., food-drug interactions).

The stated goal for the Tasigna RiskMAP is to ensure that important information on the proper use and safety profile of Tasigna is appropriately communicated to healthcare professionals and patients.

We agree with the scope and tools of the RiskMAP. Issues remaining to be resolved to allow final acceptance of the RiskMAP include:

## 1 BACKGROUND

### 1.1 INTRODUCTION

Nilotinib is a tyrosine kinase inhibitor that is available as an oral capsule formulation (200mg hard gelatin capsules). Similar to imatinib (Glivec®/Gleevec®), nilotinib is an ATP-competitive inhibitor of Bcr-Abl. According to the Sponsor, in comparison to imatinib, nilotinib has greater potency and selectivity against Bcr-Abl, the primary target in CML. It is active in vitro and in vivo against imatinib-resistant Bcr-Abl dependent myeloproliferative diseases.

An approval for nilotinib is being sought to treat Chronic Phase or Accelerated Phase Philadelphia chromosome positive CML in adult patients resistant to or intolerant to [REDACTED] prior therapy including imatinib. Nilotinib is not currently approved in any country.

### 1.2 REGULATORY HISTORY

NDA 022-068 is an application for nilotinib, a new molecular entity, to treat Chronic Phase (CP) or Accelerated Phase (AP) Philadelphia chromosome positive CML in adult patients resistant to or intolerant to [REDACTED] prior therapy including imatinib. The data have been submitted under the rolling NDA procedure. The first module of the rolling NDA was submitted on August 9, 2006. The module which completed the NDA was submitted on September 29, 2006. The indication under review in this NDA received Fast Track designation on May 11, 2006. The PDUFA goal date for the application is July 29, 2007.

## 2 METHODS AND MATERIALS

## 2.1 DATA AND INFORMATION SOURCES

The following documents were reviewed:

- Tasisna Risk Management Plan / Risk Minimization Action Plan; submitted to the NDA by Novartis 9/29/06; available in EDR.
- Tasisna Risk Management Plan / Amendments; submitted to the NDA by Novartis 6/8/07 and 6/26/07; available in EDR.
- NDA 22-068 Tasisna: CTD 2.7.4 Summary of Clinical Safety: 120-Day Safety Update, 1/16/07; available in EDR.
- Draft Tasisna labeling; submitted to the NDA by Novartis 9/29/06 and 5/3/07; available in EDR.
- Gleevec labeling approved by FDA 10/30/2006, URL accessed 7/1/07; available at [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory)

## 2.2 ANALYSIS TECHNIQUES

The Sponsor's submissions were reviewed for conformance with the concepts in the FDA Guidance for Industry, *Development and Use of Risk Minimization Action Plans (RiskMAPs)*.<sup>1</sup> The Sponsor's proposal to use labeling alone to manage some risks was compared to the use of labeling to manage risks of imatinib (Gleevec), a related drug that shares some of the risks observed with nilotinib. The Division of Drug Marketing, Advertising, and Communications (DDMAC) was consulted to review RiskMAP educational materials for promotional content.

## 3 RESULTS OF REVIEW

### 3.1 SAFETY CONCERNS

The Sponsor identified the following product risks identified through the clinical experience accumulated to date with nilotinib.

1. QTc prolongation;
2. Drug-drug interactions;
3. Food effects;
4. Hepatotoxicity;
5. Amylase and lipase elevations;
6. Ischemic myocardial events; and
7. Fetal toxicity.

Each of these is described in more detail below.

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<sup>1</sup> Available at URL [www.fda.gov/cder/guidance/6358fnl.pdf](http://www.fda.gov/cder/guidance/6358fnl.pdf)

### **3.1.1 QTc Prolongation**

The potential for Tasigna to cause ventricular repolarization abnormalities related to QT interval prolongation was identified in preclinical testing. ECG monitoring was conducted in clinical trials. As reported by the Sponsor, few patients in clinical trials developed QTc values >480 msec, and very few developed QTc values >500 msec. There were four sudden deaths in clinical studies in which a cause of death could not be established with certainty, and to which QTc prolongation may have played a role. Torsade de pointes has not been reported to date. In Phase 1, Phase 2 CML-CP, and Phase 2 CML-AP, two patients (0.4%, n=490) were reported to have a ventricular arrhythmia as a grade 3 or 4 serious adverse event and three patients (0.6%) were found to have QTcF >500msec. The pharmacology of Tasigna, including CYP3A4 inhibition of metabolism and increased serum concentration when administered with food, necessitate monitoring to minimize the potential for QT interval prolongation.

### **3.1.2 Drug-drug interaction**

Tasigna is metabolized by CYP3A4 and is also a weak inhibitor of CYP3A4. When Tasigna was co-administered with ketoconazole, a potent CYP3A4 inhibitor, the  $C_{max}$  of Tasigna increased by 84% and the AUC increased by 3-fold. Concurrent treatment of Tasigna with strong CYP3A4 inhibitors and/or inducers should be avoided. Additionally, when midazolam, a CYP3A4 substrate, was co-administered with Tasigna, there was a 30% increase in the midazolam AUC. In vitro, Tasigna was a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2D6. Caution should be exercised when co-administering Tasigna with substrates of these enzymes having a narrow therapeutic index.

### **3.1.3 Food-drug interactions**

The absorption of Tasigna is increased if taken with food, resulting in higher serum concentrations. The overall exposure and  $C_{max}$  of Tasigna increased by 29% and 55%, 15% and 33%, and 82% and 112% relative to overnight fasting when given 30 minutes after a light meal, 2 hours after a light meal, or 30 minutes after a high fat meal, respectively. Grapefruit juice and other foods known to inhibit CYP3A4 should not be consumed by patients taking Tasigna.

### **3.1.4 Hepatotoxicity**

Hepatotoxicity, including increased transaminases and increased bilirubin, were reported in about 10% of patients treated with nilotinib. About half of the patients treated with nilotinib greater than 400mg daily experienced Grade 1 liver function abnormalities. Grade 3/4 abnormalities were uncommon. In clinical trials, this toxicity was managed with dose reduction.

### **3.1.5 Elevation in Serum Amylase and Lipase and Pancreatitis**

Serum amylase and lipase elevations were observed in the nilotinib clinical trials. Serum lipase elevations occurred in about 40% of CML CP and AP study patients. Clinical pancreatitis occurred in < 1% of patients receiving nilotinib.<sup>2</sup> Clinical pancreatitis generally occurred in patients with a prior history of pancreatitis.

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<sup>2</sup> CTD 2.7.4 Summary of Clinical Safety: 120 day Safety Update, pgs 111-2.

### ***3.1.6 Ischemic Myocardial Events***

Ischemic myocardial injury secondary to reduced coronary perfusion following the use of nilotinib was suggested by preclinical experiments using the SCREENIT assay. According to the Sponsor, these experiments were inconclusive due to precipitation of the test agent, nilotinib. Creatine kinase and troponin levels were monitored in clinical trials due to the potential for myocardial injury. However, the Sponsor reports the results of the lab monitoring have been inconclusive. Clinical events, including myocardial infarction, have been reported in patients receiving nilotinib.

### ***3.1.7 Fetal Toxicity***

Nilotinib may cause fetal harm when administered to a pregnant woman. Studies in animals showed no teratogenicity, however, nilotinib was embryotoxic and fetotoxic at doses associated with maternal toxicity. It is recommended that women of child bearing potential use effective contraception while being treated with nilotinib.

## **3.2 PROPOSED RISKMAP**

12 Page(s) Withheld

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Draft Labeling

Deliberative Process

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7/12/2007 01:37:20 PM  
DRUG SAFETY OFFICE REVIEWER

Ellis Unger  
7/12/2007 02:10:34 PM  
MEDICAL OFFICER

**Jamison, Janet**

---

**From:** Jamison, Janet  
**Sent:** Thursday, September 27, 2007 10:14 AM  
**To:** 'darshan.wariabharaj@novartis.com'; 'robert.miranda@novartis.com'  
**Subject:** N22-068: Summary "Grp B" Responders- FDA Request for Information 9-27-07

Bob, Darshan,

The reviewers have requested the following from the 9-19-07 data submission:

In the third slide, CML-AP, 6 HR responses have been reported, but only 5 patients described. Please clarify.

Janet

---

**From:** darshan.wariabharaj@novartis.com [mailto:darshan.wariabharaj@novartis.com]  
**Sent:** Wednesday, September 19, 2007 1:24 PM  
**To:** Jamison, Janet  
**Subject:** Re: N22-068: Narrative Summary "Grp B" Responders/Summary of Data Presented At ASCO 2007

Hi Janet:

Further to my e-mail of Sep.18, please find attached a narrative summary of all "Grp B" responders in this data set. Please inform the reviewers that in the patient summaries, when FISH is not mentioned this means the response is based on cytogenetics.

In addition, a copy of the summary of the data that was presented at ASCO 2007 is provided. This data was discussed at our Sep.13 telecon. Note: Although this was previously provided by Bob we are providing again for the reviewers convenience.

Feel free to e-mail me if you have any questions.

Regards,

Darshan Wariabharaj  
Associate Director - Drug Regulatory Affairs Oncology  
Novartis Pharmaceuticals Corporation  
Phone: 8627789470  
Fax: 973-781-5217  
Email : darshan.wariabharaj@novartis.com

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Janet Jamison  
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**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

**Memorandum**

**From:** Janet Jamison, R.N., R.P.M.

**To:** John Jenkins, M.D.

**Subject:** Regulatory Briefing Meeting Summary

**Sponsor:** Novartis Pharmaceuticals

**Product:** Tassigna™ (nilotinib) capsules

**Meeting Chair:** John Jenkins, M.D.

**Date, Location, & Time of Meeting:** August 17, 2007  
WO CSU, Conference Room 2046  
1:00 p.m. – 3:00 p.m.

**Purpose:** NDA22-068/ Tassigna (nilotinib)/ QT Prolongation and Unexplained Sudden Deaths: To discuss QT prolongation and unexplained sudden deaths reported in one single-arm clinical trial; whether they represent an unacceptable level of risk for approval of this agent in the chronic myelogenous leukemia (CML)-chronic Phase (CP) and accelerated Phase (AP) populations in light of current approved therapy for this indication and whether the single-arm trial permits an adequate assessment of these safety signals. If these do not represent an unacceptable level of risk for approval, should the labeling include a black box warning?

**FDA Attendees:**

Renata Albrecht	Ann Farrell
Thushi Amini	Joel Schiffenbauer
Badrul Chowdhury	Shwu Luan Lee
Charles Ganley	Joyce Weaver
Stephen Grant	Susan McCune
Shiew-Mei Huang	Jeanine Best
John Jenkins	Pravin Jadhav
Hylton Joffe	Rajeshwari Sridhara
Robert Justice	Xiaoping (Janet) Jiang
Richard Pazdur	Chia-wen Ko
Nam Atiqur Rahmn	Edvardas Kaminskas
Rosemary Roberts	Ruyi He
George Rochester	John Leighton
Curtis Rosebraugh	Diane Spillman
Daniel Shames	Joanne Zhang
Sol Sobel	Janet Jamison
Norman Stockbridge	Virginia Elgin
Ana Szarfman	Maitreyee Hazarika
Bob Temple	Qi Liu
Karen Weiss	Brian Booth
Ramzi Dagher	Roshni Ramchandani
Diane Wysowski	

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**1.0 PRODUCT AND PROPOSED INDICATION FOR USE**

Tasigna® (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.

**2.0 REGULATORY CONCERN:**

QT prolongation and unexpected sudden deaths seen with nilotinib were identified during the review of the NDA. The review team has concerns that the single-arm trial design does not permit an adequate assessment of these safety signals. Consultation from the panel was requested to discuss whether the risk/benefit analysis warrants approval. Three questions were presented to the panel for further discussion:

1. Is there enough evidence to suggest that QT prolongation may have played a role in the sudden deaths observed?

2. Since nilotinib was not evaluated in a randomized trial, it is difficult to interpret the safety data. Should the sponsor be required to conduct a randomized controlled trial prior to approval?
3. If approved, should there be a Black Box Warning for the events of sudden death and QT prolongation, and include risk factors for QT prolongation?

### **3.0 BACKGROUND (See Attachment 2)**

### **4.0 DISCUSSION**

The meeting started with brief opening remarks by Dr. John Jenkins, followed by an introduction of the purpose for the meeting by Dr. Robert Justice. Dr. Maitreyee Hazarika, medical reviewer of the application, gave an overview and presented the efficacy and safety of nilotinib. Dr. Ramchandani presented the QT clinical evaluation. The presentation concluded with the three questions (stated above) on which the Division was seeking advice. The meeting was then opened to the panel for discussion.

Regarding the first question, the panel noted that some cases are very convincing that QT prolongation may have contributed to sudden deaths. It was also noted that the death rate observed seemed rather high compared to other drugs that have this magnitude of QT prolongation. It was stated that other alternative cardiovascular risk factors need to be carefully considered in the final analysis, including underlying disease, since one cannot attribute the sudden deaths solely to QT effects.

Regarding the second question, there was consensus among the panel that the current efficacy data are not compelling. The overall discussion argued for more data before approval. The panel agreed that safety and effectiveness in this patient population would need to be assessed in a randomized clinical trial. The design could be a dose-response trial or an active control trial using the currently approved second-line therapy, dasatinib. It was also recommended that nilotinib be evaluated as third-line therapy for patients who have failed dasatinib and imatinib therapy or who have experienced unacceptable toxicity on imatinib and dasatinib, since this is the setting where the drug would likely be used if approved.

Regarding the third question, the panel stated that an Advisory Committee could be useful in determining the need for a black box warning. Dr. Pazdur pointed out that the Division is scheduled to meet with the sponsor later today regarding these safety concerns. Their comments and further analysis would first be taken into consideration by the Division. The consensus of the panel was that yes, if nilotinib is approved there should be a black box warning for sudden death and QT prolongation. However, it was

noted that based on past experience with cardio-renal drug products, compliance may be an issue despite black box warnings and recommendations for cardiac monitoring.

## **5.0 ISSUES REQUIRING FURTHER DISCUSSION**

None stated.

## **6.0 ACTION ITEMS**

- The nilotinib safety concerns could be discussed at a meeting of the Oncologic Drugs Advisory Committee.
- The Division will discuss the safety concerns with the sponsor and consider their analysis.
- The consensus of the panel was:
  - Yes, there is evidence that QT prolongation may have caused sudden death in some of the cases.
  - Nilotinib should not be approved without further data from a randomized trial.
  - If nilotinib is approved there should be a black box warning for sudden death and QT prolongation.

## **7.0 ATTACHMENTS AND HANDOUTS**

**Attachment 1 Regulatory Briefing Agenda**  
**Attachment 2 DDOP Regulatory Briefing Document**  
**Attachment 3 DDOP Slide Presentation**  
**Attachment 4 Meeting Attendee List**

**Regulatory Briefing  
August 17, 2007**

<b>Subject:</b>	N22-068: "Tasigna (nilotinib): QT Prolongation and Unexplained Sudden Deaths"		
<b>Purpose:</b>	To discuss the unexplained sudden deaths and QT prolongation events reported in clinical trials and whether they represent an unacceptable level of risk for approval of this agent in the CML CP and AP population in light of current approved available therapy for this indication. If these do not represent an unacceptable level of risk for approval, should the labeling include a black box warning		
<b>Meeting:</b>	Regulatory Briefing		
<b>Meeting Date:</b>	August 17, 2007		
<b>Meeting Time:</b>	1:00 p.m. – 3:00 p.m.		
<b>Meeting Location:</b>	CSU 2046 with videoconferencing		
<b>Chair:</b>	John Jenkins, M.D.		
<b>Facilitator:</b>	Thushi Amini		
<b>Project Manager:</b>	Janet Jamison		
<b>Time</b>	<b>Item</b>	<b>Agenda Item</b>	<b>Presenter</b>
5 min.	1	Opening Remarks	John Jenkins, M.D.
5 min	2	Introduction	Robert L. Justice, M.D.
25 min	3	Clinical Summary	Maitreyee Hazarika, MD
10 min	4	QT Prolongation; Clinical Evaluation	Roshni Ramchandani, PhD
45 min	5	Discussion	Panel
15 min	6	Wrap-Up	John Jenkins, M.D.

Following the presentations, the following questions will be discussed:

1. Is there enough evidence to suggest that QT prolongation may have played a role in the sudden deaths observed?
2. Since nilotinib was not evaluated in a randomized trial, it is difficult to interpret the safety data. Should the sponsor be required to conduct a randomized controlled trial prior to approval?
3. If approved, should there be a Black Box Warning for the events of sudden death and QT prolongation, and include risk factors for QT prolongation?

**REGULATORY BRIEFING DOCUMENT**  
**NILOTINIB: QT PROLONGATION AND UNEXPLAINED SUDDEN DEATHS**

**Regulatory Briefing: 8/17/07**  
**Office of Oncology Drug Products**  
**Division of Drug Oncology Products**  
**Nilotinib Review Team**

<b>NDA</b>	22-068
<b>Established name</b>	Nilotinib
<b>Proposed Trade Name</b>	Tasigna®
<b>Mechanism</b>	Bcr-Abl tyrosine kinase inhibitor
<b>Sponsor</b>	Novartis Pharmaceuticals Inc.
<b>Proposed Indication</b>	Chronic Myelogenous Leukemia (chronic phase and accelerated phase) resistant to or intolerant of imatinib mesylate
<b>PDUFA Goal Date</b>	10/28/2007
<b>Approved Therapy</b>	Dasatinib/Sprycel®

## **1. INTRODUCTION**

The objective of this Regulatory Briefing is to seek advice on the safety issues of QT prolongation and unexpected sudden deaths seen with nilotinib that were identified during the review of the NDA. We are concerned that the single-arm trial design does not permit an adequate assessment of these safety signals. We are asking the panel to discuss whether the risk/benefit analysis warrants approval. If approval is recommended, should there be a Black Box Warning for these events in the label, including the use of concomitant medications that prolong QT interval and cause CYP inhibition? This document provides the background material for the meeting.

Nilotinib (Tasigna®) is a highly selective inhibitor of the tyrosine kinase activity of the Bcr-Abl oncoprotein. This protein is the product of the BCR-ABL fusion gene, which results from a reciprocal chromosome 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.

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

The Applicant has submitted NDA 22-068 for the following proposed indications:  
*“Tasigna® (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”*

If approved, nilotinib will be the second marketed drug in this class of drugs for these indications. Dasatinib (Sprycel®) received accelerated approval in June 2006 for use in the treatment of adults with chronic phase (CP), accelerated phase (AP), myeloid or lymphoid blast (MB or LB) phase chronic myeloid leukemia (CML) and Ph+ ALL with resistance or intolerance to prior therapy including imatinib mesylate. The preliminary results of two randomized trials of dasatinib were submitted to the NDA in June 2007 and are currently under review.

## 2. BACKGROUND

CML is a clonal myeloproliferative disorder of the hematopoietic stem cell, characterized by a reciprocal translocation t(9;22) which forms the Philadelphia chromosome (Ph<sup>+</sup>) and creates a novel fusion gene *bcr-abl*. CML accounts for approximately 15 to 20 percent of cases of leukemia in adults. It has an annual incidence of 1 to 2 cases per 100,000, with a slight male predominance. The median age at presentation is approximately 50 years for patients enrolled on clinical studies, but the actual median age from cancer registry data may be 60 years of age or older.

CML has a triphasic clinical course: an initial indolent chronic phase (CP), which is present at the time of diagnosis in approximately 85 percent of patients; an accelerated phase (AP), in which neutrophil differentiation becomes progressively impaired and leukocyte counts are more difficult to control with myelosuppressive medications; and a terminal blast crisis (BC), a condition resembling acute leukemia in which myeloid or lymphoid blasts fail to differentiate. CML inevitably progresses to blast crisis within an average of three to five years after diagnosis, and three to eighteen months after onset of the accelerated phase. Median survival is 4 to 6 years, with a range of less than 1 year to more than 10 years.

Imatinib mesylate, an inhibitor of the BCR-ABL tyrosine kinase, received FDA approval in May 2001. Imatinib resistance can be defined as lack of a complete hematologic response in patients with CP-CML or as a failure to return to CP for patients with CML in AP or BP. The majority of patients with imatinib-resistant CML have secondary *bcr-abl* mutations which either impair the ability of the kinase to adopt the closed conformation to which imatinib binds or directly interfere with drug binding.

The estimated 2-year incidence of imatinib resistance is 10 to 20% in CML-CP post-interferon- $\alpha$  failure and 40 to 50% in CML-AP. Dasatinib (Sprycel®) was approved in June 2006 as a treatment for patients with imatinib-resistant CML-CP, AP, BC and Ph<sup>+</sup> ALL.

### 3. PHARMACOLOGY AND TOXICOLOGY

In nonclinical studies, pro-arrhythmic effects of nilotinib were observed *in vitro* as inhibition of hERG tail current (IC<sub>50</sub> at 0.13  $\mu$ M), prolongation of action potential duration (APD), and induced triangulation and beat-to-beat variability in rabbit hearts. Coronary vasoconstrictive effects were illustrated in isolated human coronary arteries and *in vivo* in rabbit hearts.

Nilotinib-induced histopathological changes in the heart included: minimal cardiomyopathy in rats (0.6 fold the AUC in patients at the recommended human dose); minimal focal mesothelial cell proliferation, and minimal to slight coronary medial hypertrophy in dogs (0.3 fold the AUC in patients at the recommended human dose); and slight hemorrhage in monkeys (0.7 fold the AUC in patients at the recommended human dose). Accumulation was observed after repeat dose administration (4 to 39 weeks) in dogs and monkeys (t<sub>1/2</sub> about 24 h).

### 4. CLINICAL PHARMACOLOGY

#### 4.1 QT Interval Prolongation

Nilotinib has been shown to prolong cardiac ventricular repolarization as measured by the QT interval on the surface ECG in a concentration-dependent manner in both healthy volunteers and patients with CML.

A dedicated QT study was conducted in healthy volunteers; however, due to lack of tolerability the highest mean nilotinib exposure achieved (1669 ng/ml) was 26% lower than the mean exposure seen in patients administered the clinical dose of 400 mg BID (steady-state C<sub>max</sub>=2260 ng/ml) in the phase 2 study. The maximum increase in the placebo-corrected mean change in QTcF from baseline was observed at T<sub>max</sub> (6 hours post-dose) and was 14 ms (upper 95% confidence bound: 21 ms).

At the mean steady-state C<sub>max</sub> of 2260 ng/ml, using the concentration - QT relationship derived from the QT study, the mean placebo and baseline-adjusted QTcF would be 16 ms (upper 95% confidence bound:20 ms).

Several factors such as CYP3A4 inhibitors, a high fat meal, hepatic impairment, electrolyte abnormalities, and concomitant use of QT prolonging drugs could further prolong the QT interval significantly.

#### 4.2 Drug Interactions

Nilotinib undergoes extensive metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 alter nilotinib concentrations significantly. In healthy subjects, co-administration of nilotinib with ketoconazole, a strong inhibitor of CYP3A4, increased nilotinib C<sub>max</sub> by 80% and AUC by 3-fold on average. Therefore, patients who take strong CYP3A4 inhibitors concomitantly with nilotinib are likely to attain nilotinib exposure that is associated with an increased risk for QT interval prolongation.

#### **4.3 Food Effects**

Nilotinib is absorbed following oral administration. The median time to reach C<sub>max</sub> of nilotinib was 3 hours. The bioavailability of nilotinib is increased by food. Compared to the fasted state, the C<sub>max</sub> and AUC was increased by 112% and 82%, respectively, when the dose was given 30 minutes after a high fat meal. Therefore, patients who take nilotinib with a meal may have a higher nilotinib exposure which may be associated with an increased risk for QT interval prolongation. To minimize the effect of food on nilotinib bioavailability, the proposed package insert recommends that nilotinib should be taken at least 2 hours after food intake, and food intake should be avoided for 1 hour after drug administration.

#### **4.4 Hepatic Impairment**

Nilotinib has not been investigated in patients with hepatic impairment. Given the fact that metabolism of nilotinib is mainly hepatic, a decrease in nilotinib clearance is possible for patients with hepatic impairment. Therefore, patients with hepatic impairment may have a higher exposure of nilotinib which may be associated with an increased risk for QT interval prolongation.

#### **4.5 UGT1A1 Pharmacogenomics**

In a pharmacogenetic analysis of UGT1A1 polymorphism and hyperbilirubinemia, it was observed that patients with UGT1A1 7/7 genotype treated with nilotinib were observed to have increased elevations in bilirubin relative to the 6/6 or 6/7 patients. Large increases in  $\geq$  grade 3 hyperbilirubinemia were seen in the 7/7 genotype (58%) relative to 6/7 (4.5%) or 6/6 (4.9%) genotypes. Only slight increases were seen for  $\geq$  grade 3 ALT increases. Other transaminases (AST or ALP) did not recapitulate the changes observed for ALT.

The study results indicate that UGT1A1 7/7 genotype patients are at an increased risk for hyperbilirubinemia.

## **5. CLINICAL STUDY**

## 5.1 Study Design

Study 2101 was a single, open-label, multicenter study which lacked a comparator arm. All patients received nilotinib. The single Phase 1/2 study had six cohorts of which two cohort subsets were the study populations in the indication, i.e., patients with CML-CP and CML-AP who were resistant or intolerant to prior imatinib without other tyrosine kinase inhibitors. The two populations relevant for the indications were Group A patients in Arms 3 and 4 as shown in Table 1 below. Group A consisted of patients who had no prior treatment with other tyrosine kinase inhibitors except imatinib. Group B consisted of patients who had prior treatment with other tyrosine kinase inhibitors in addition to imatinib.

**Table 1: Study 2101, Phase 2 Cohorts**

Cohort 1: Relapsed/refractory Ph+ ALL
Cohort 2: Imatinib-resistant or -intolerant Ph+ CML-BC (Group A and Group B)
<b>Cohort 3: Imatinib resistant/intolerant Ph+ CML-AP (Group A or Group B)</b>
<b>Cohort 4: Imatinib resistant/intolerant Ph+ CML-CP (Group A or Group B)</b>
Cohort 5: Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia (HES/CEL)
Cohort 6: Systemic Mastocytosis

## 5.2 CML-CP Efficacy

At the time of data cut-off, 280 CML-CP patients evaluable for efficacy were enrolled.

The primary efficacy endpoint in chronic phase CML was unconfirmed major cytogenetic response (MCyR), defined as elimination (complete cytogenetic response) or reduction to <35% Ph+ metaphases (partial cytogenetic response) of Ph+ hematopoietic cells. The rates of response for CML-CP after FDA reviewer adjudication are reported in Table 2 below. The responses occurring with dasatinib as stated in the label are also shown in the same table.

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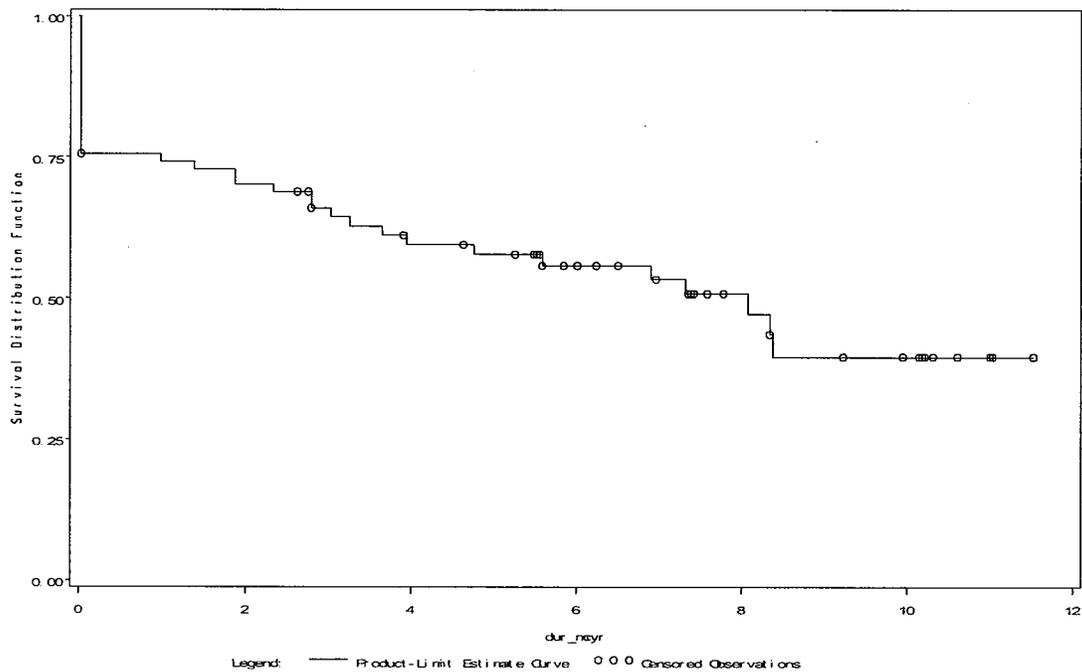
**Table 2: Efficacy CML-CP**

	<b>Nilotinib CML-CP N=280 %</b>	<b>Dasatinib* CML-CP N=186 %</b>
<b>Major Cytogenetic Response (unconfirmed)</b>	<b>33</b>	<b>45</b>
Complete	23	33
Median Duration	8.3 months	Not reached
Complete hematologic response	50	90

\* Source: Dasatinib PI

There was limited follow-up of patients in the initial submission and also in the 120-day safety/efficacy update. Duration of response was based on a follow up of at least 6 months in all patients. Figure 3 describes the FDA analysis of duration for the primary endpoint of major cytogenetic response.

**Figure 3: Duration Unconfirmed MCyR**



### 5.3 CML-AP Efficacy

At the time of data cut-off, 105 CML-AP patients evaluable for efficacy were enrolled.

The primary efficacy endpoint in accelerated phase CML was confirmed major hematologic response (HR), defined as either a complete hematologic response or no evidence of leukemia. The rates of response for CML-AP after FDA reviewer adjudication are reported in Table 3. The responses occurring with dasatinib as stated in the label are also shown.

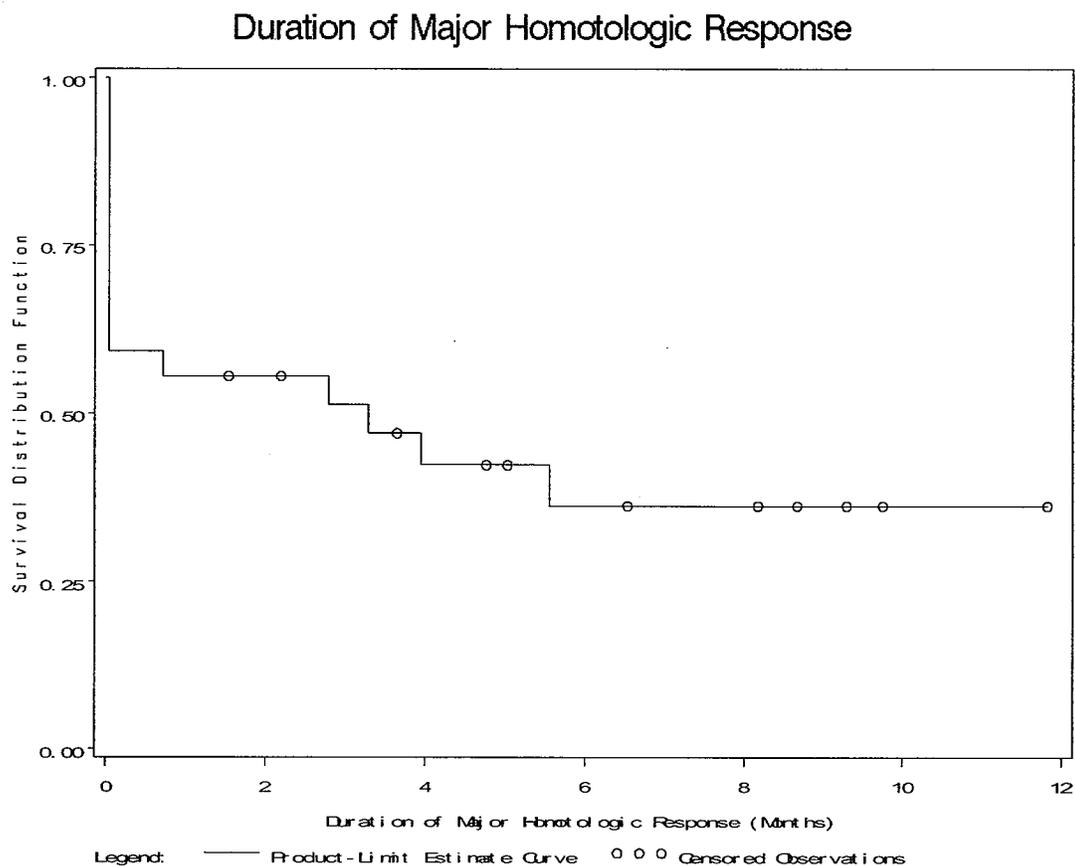
**Table 3: Efficacy CML-AP**

	<b>Nilotinib</b>	<b>Dasatinib*</b>
	<b>CML-AP</b>	<b>CML-AP</b>
	<b>N=105</b>	<b>N=107</b>
	<b>%</b>	<b>%</b>
<b>Major Hematologic Response (confirmed)</b>	<b>27</b>	<b>59</b>
Complete hematologic response	18	33
No evidence of leukemia	9	26
Median Duration	3.28	Not reached
<b>Major Cytogenetic Response (unconfirmed)</b>	<b>16</b>	<b>31</b>
Complete	9	21

\* Source: Dasatinib PI

There was limited follow-up of patients in the initial submission and also in the 120-day safety/efficacy update. The duration of response was based on a follow-up of at least 4 months in all patients. Figure 4 describes the FDA analysis of duration for the primary endpoint of confirmed major hematologic response.

**Figure 4: Duration Confirmed MHR**



## 6. SAFETY

The clinical database which contributes to the safety profile of nilotinib in imatinib-resistant or -intolerant CML-CP and CML-AP patients consists mainly of a single, currently ongoing, Phase 1/2, open-label study, Study 2101. Supportive data are derived from the Phase 1 portion of the study and the other Phase 2 cohorts.

**Table 4: Summary of Safety Populations**

<b>Study Number/Phase</b>	<b>Population</b>	<b>Number of Patients</b>
2101 Phase 2	Imatinib resistant/intolerant Ph+ CML CP with prior imatinib (Cohort 4, Group A)	318
2101 Phase 2	Imatinib resistant/intolerant Ph+ CML AP with prior imatinib (Cohort 3, Group A)	120
2101 Phase 1	Imatinib resistant patients	119
	CML-CP	27
	CML-AP	46
	Others	46
2101 Phase 2 Other Cohorts	Imatinib resistant/intolerant patients with Ph+ CML-CP with prior TKIs other than imatinib (Cohort 4, Group B)	23
	Ph+ CML-AP with prior TKIs other than imatinib (Cohort 3, Group B)	13
	Ph+ CML-BC with prior TKIs other than imatinib (Cohort 2, Groups A&B)	159
1101	Japanese patients with CML-CP, AP, BC or ALL	11

### 6.1 Deaths

There were 13 deaths during the nilotinib study (i.e., patients who were on treatment or within 30 days after discontinuing drug) reported by the applicant in the CML-CP and CML-AP patient populations of 438 patients. Two of these deaths were sudden deaths and are described in Section 6.2.

In contrast, there were seven deaths during the dasatinib study (i.e., patients who were on treatment or within 30 days after discontinuing drug) in the CML-CP and CML-AP populations which included 226 patients. There were two sudden deaths reported in the Dasatinib Clinical Review, NDA 21-986, both not considered related to QTc prolongation. These sudden deaths were not reported in the dasatinib PI.

### 6.2 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. There was a relative early occurrence of some of these events and the cause of death uncertain in some patients. Several patients were on concomitant medications which either prolonged QT interval or were associated with TdP or were CYP inhibitors.

Table 5 shows the available details of the cause of death for the six sudden deaths in the safety population.

**Table 5: Overview of Sudden Deaths in Study 2101 \***

Patient ID/ Center	Age/ Gender	Study/ Dose	Day of Death	Details of Cause of Death
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 USA	31/M	Phase 1 CML AP 400 bid	177	Day 177, found dead at home. Autopsy: "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.
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\*The applicant has been asked to clarify and provide more details regarding issues surrounding these deaths

According to the 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 block, 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 > 450 msec on screening ECG (using the QTcF formula), and myocardial infarction within 3 months prior and angina pectoris.

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

Table 6 shows the available details of the four sudden deaths in the expanded access protocol or with single patient compassionate use.

**Table 6: 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 800 qd	150	Day 150 found dead in bed; QTc 456 2 months prior; treatment with moxifloxacin for 1 week prior to death for upper respiratory infection (moxifloxacin prolongs QT).

\*The applicant has been asked to clarify and provide more details regarding issues surrounding these deaths

### 6.3 Non-laboratory Adverse Events

The data below reflect exposure to nilotinib in 438 patients with CML-CP and CML-AP from the Phase 2 portion of Study 2101. The median exposure in the 318 patients with CML-CP was 245 days (range: 1-502). The median exposure in the 120 patients with CML-AP was 137.5 days (range: 2-503).

The most frequently reported all grade non-laboratory adverse events (AEs) in the CML-CP patients were rash (33.6%), nausea (31.1%), headache (30.8%), pruritus (28.6%), fatigue (28.3%), diarrhea (22.6%), abdominal pain/upper (21.4%), vomiting (21.1%), constipation (20.8%), arthralgia (18.1%), cough (17%), nasopharyngitis (15.4%), myalgia (14.5%), pyrexia (14.2%), asthenia (13.8%), extremity pain (13.2%), bone pain (11.3%), peripheral edema (10.7%), muscle spasms (10.7%) and back pain (10.4%).

The commonest all grade non-laboratory AEs in the CML-AP patients were rash (28.3%), pyrexia (24.2%), abdominal pain/ upper (22.5%), headache (21.7%), pruritus (20%), diarrhea (19.2%), constipation (18.3%), nausea (18.3%), arthralgia (15.8%), extremity pain (15.8%), fatigue (15.8%), myalgia (15%), muscle spasms (14.2%), bone pain (13.3%), cough (12.5%), back pain (11.7%), asthenia (10.7%), peripheral edema (10.8%), nasopharyngitis (10.8%), vomiting (10%) and anorexia (10%).

The commonest Grade 3 and 4 non-laboratory AEs reported in the CML-CP patients were diarrhea (2.8%), headache (2.8%), arthralgia (2.2%), angina pectoris (1.9%), 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%), dyspnea (1.3%), extremity pain (1.3%).

The commonest Grade 3 and 4 non-laboratory AEs reported in the CML-AP patients were febrile neutropenia (2.5%), abdominal pain (2.5%), dyspnea (2.5%), angina pectoris (1.7%), diarrhea (1.7%), pyrexia (1.7%), headache (1.7%), extremity pain (1.7%).

The incidences of grade 3 and 4 non-laboratory AEs for nilotinib based on the FDA reviewer's analyses are shown in Table 7. Those occurring with dasatinib as stated in the label are also shown.

#### Table 7: Non-laboratory Grade 3 and 4 Adverse Reactions

	Nilotinib		Dasatinib <sup>#</sup>	
	CML-CP N=318 %	CML-AP N=120 %	CML-CP N=488 %	CML-AP N=186 %
<b>Angina pectoris</b>	2	2	*	*
<b>Myocardial infarction</b>	1	1	*	*
<b>Hepatic failure, cytolytic hepatitis, hepatotoxicity</b>	1	1	*	*
<b>Syncope<sup>1</sup></b>	2	1	*	*
<b>Skin Rash<sup>2</sup></b>	3	0	1	1
<b>Arrhythmias<sup>3</sup></b>	1	1	2	1
<b>Infection</b>	3	6	4	8
<b>Hemorrhage</b>			3	18
Gastrointestinal	12	2	2	12
CNS Bleeding	1	2	0	1
<b>Fluid Retention</b>	<1	0	6	6
Superficial edema	0	0	0	2
Pleural effusion	<1	0	3	3
Other fluid retention	0	0	4	4
Generalized edema	0	0	1	0
CHF/cardiac dysfunction	0	1	3	1
Pericardial effusion	<1	0	1	1
Pulmonary edema	1	1	1	2
Ascites	0	0	0	1
<b>Febrile neutropenia</b>	1	3	2	11
<b>Diarrhea</b>	3	2	3	10
<b>Headache</b>	3	2	2	2
<b>Musculoskeletal pain<sup>4</sup></b>	5	2	2	3
<b>Pyrexia</b>	1	2	1	5
<b>Fatigue</b>	1	<1	2	4
<b>Abdominal pain</b>	1	3	1	2
<b>Dyspnea</b>	1	3	5	7

<sup>#</sup> Source: Dasatinib PI, Dose 70 mg PO BID

\* Not reported in dasatinib label

<sup>1</sup> Skin rash includes 'rash', 'generalized rash', 'pruritic rash', 'exfoliative rash' and 'allergic dermatitis'.

<sup>2</sup> Syncope includes 'syncope' and 'syncope vasovagal'.

<sup>3</sup> Arrhythmias include 'ventricular tachyarrhythmias' and 'supraventricular tachyarrhythmias'.

<sup>4</sup> Musculoskeletal pain includes 'arthralgia', 'myalgia' and 'pain in extremity'.

## 6.4 Laboratory Adverse Events

Thrombocytopenia, neutropenia, and anemia were the most frequently reported grade 3 and 4 laboratory abnormalities in CML-CP and CML-AP patients without prior TKI

treatment other than imatinib. The incidences of treatment-emergent CTC grade 3-4 thrombocytopenia in CML-CP and CML-AP patients were 27% and 40%, respectively. The incidences of treatment-emergent CTC grade 3-4 neutropenia in CML-CP and CML-AP patients were 28% and 38%, respectively. The incidences of treatment-emergent CTC grade 3-4 anemia in CML-CP and CML-AP patients were 9% and 28%, respectively.

Elevations in serum lipase, not observed in preclinical toxicology studies, were an unexpected finding in this patient population. The incidence of asymptomatic serum lipase laboratory abnormalities far exceeds the incidence of these abnormalities seen in the presence of clinical symptoms such as abdominal pain or a diagnosis of pancreatitis. In CML-CP patients, all grades and grade 3-4 treatment-emergent serum lipase elevations occurred in 40.3% and 14.5% of patients, respectively. In CML-AP patients, all grades and grade 3-4 treatment-emergent serum lipase elevations occurred in 35.8% and 15.8% of patients, respectively. Pancreatitis occurred in 3 (0.9%) and 1 (0.8%) of CML-CP and CML-AP patients without prior TKI treatment other than imatinib, respectively. One patient (patient 0504\_03006) discontinued study drug on day 128 due to pancreatitis which was suspected related to study drug. Patient died on day 316.

In CML-CP patients, all grades and grade 3-4 treatment-emergent total serum bilirubin elevations occurred in 69.8% and 8.8% of patients, respectively. In CML-AP patients, all grades and grade 3-4 treatment-emergent total serum bilirubin elevations occurred in 65.8% and 10% of patients, respectively.

All grades and grade 3-4 treatment-emergent serum ALT elevations occurred in 61.9/3.8% of CML-CP patients, respectively. All grades and grade 3-4 treatment-emergent serum AST elevations occurred in 46.2/1.3% of CML-CP patients, respectively. All grades and grade 3-4 treatment-emergent serum ALT elevations occurred in 51.7/2.5% of CML-AP patients, respectively. All grades and grade 3-4 treatment-emergent serum AST elevations occurred in 35.8/0.8% of CML-AP patients, respectively.

The overall incidence of all grades of hyperglycemia was 66.7% in CML-CP patients and 54.2% in CML-AP patients. The incidence of grade 3 or 4 hyperglycemia was 11% and 5% in CML-CP and CML-AP patients respectively.

Electrolyte abnormalities occurred in both CML-CP and CML-AP patients. All grades and grade 3/4 hypophosphatemia occurred in 42.8%/10.1% CML-CP patients and in 40%/12.5% CML-AP patients. All grades and grade 3/4 hypocalcemia occurred in 40.9%/0.6% CML-CP patients and in 52.5%/4.2% CML-AP patients. All grades and grade 3/4 hyponatremia occurred in 22%/3.1% CML-CP patients and in 25.8%/2.5% CML-AP patients. All grades and grade 3/4 hypokalemia occurred in 18.6%/1.3% CML-CP patients and in 22.5%/5% CML-AP patients. All grades and grade 3/4 hypomagnesemia occurred in 12.9%/0% CML-CP patients and in 14.2%/0% CML-AP patients.

The incidences of clinically relevant grade 3 and 4 laboratory abnormalities related to nilotinib based on the FDA reviewer’s analyses are shown in Table 8. Those of dasatinib as stated in the label are also shown.

**Table 8: Incidence of Clinically Relevant Grade 3 and 4 Laboratory Abnormalities**

	Nilotinib		Dasatinib <sup>#</sup>	
	CML-CP N=318 %	CML-AP N=120 %	CML-CP N=488 %	CML-AP N=186 %
<b>Thrombocytopenia</b>	27	40	48	83
<b>Neutropenia</b>	28	38	49	74
<b>Anemia</b>	9	28	18	70
<b>Elevated lipase</b>	15	16	*	*
<b>Elevated bilirubin</b>	9	10	<1	1
<b>Elevated AST/ALT</b>	5	4	2	6
<b>Elevated alk phos</b>	1	3	*	*
<b>Hyperglycemia</b>	11	5	*	*
<b>Hypophosphatemia</b>	10	13	11	13
<b>Hypocalcemia</b>	1	4	2	9
<b>Hypokalemia</b>	4	3	*	*
<b>Hyponatremia</b>	3	3	*	*

<sup>#</sup> Source: Dasatinib PI, Dose 70 mg PO BID

\* Not reported in dasatinib label

## 7. QUESTIONS FOR THE PANEL

1. Is there enough evidence to suggest that QT prolongation may have played a role in the sudden deaths observed?
2. Since nilotinib was not evaluated in a randomized trial, it is difficult to interpret the safety data. Should the sponsor be required to conduct a randomized controlled trial prior to approval?
3. If approved, should there be a Black Box Warning for the events of sudden death and QT prolongation, and include risk factors for QT prolongation?

15 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative-7

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/s/

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Robert Justice  
9/11/2007 02:51:14 PM

## Atkins, Brenda J

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**From:** Atkins, Brenda J  
**Sent:** Thursday, August 02, 2007 5:08 PM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22-068 FDA Request re. Certain Patients

**Importance:** High  
**Sensitivity:** Confidential

Bob:

Please provide clarifications on the following patients:

1. Please explain why patient #0303\_01001 was treated with Pantoprazole despite the concomitant medications precautions stated in the protocol? Were ECG s obtained after initiating therapy as stated in the protocol? If so, please provide the ECG results.
2. Patient 0303\_01001 had hypokalemia on day -1. Please clarify whether the patient received potassium supplementation and specify the potassium level obtained before initiating therapy with nilotinib.
3. Please provide the most recent QTcF interval for patient 0501\_00103. Please clarify whether the patient received potassium supplementation for hypokalemia on day 183 and specify the potassium level obtained before initiating therapy with nilotinib.
4. Please explain why patient 0304\_05001 was on Verapamil and when Norepinephrine was administered. Was there an overlap between the use of these two drugs along with nilotinib?
5. Please provide the "high" level of methadone found in patient #0502\_00122? Please provide the most recent electrolyte levels and QTcF interval for this patient. Please clarify whether the autopsy included screening for other drugs and provide the results.
6. Please explain why patient #514\_00015 was treated with Fluconazole despite the concomitant medications precautions stated in the protocol? Were ECG s obtained after initiating therapy as stated in the protocol? If so, please provide the ECG results.
7. Please explain why patient #307-1 was treated with Moxifloxacin and Pantoprazole despite the exclusion criteria and concomitant medications precautions stated in the protocol? Were ECG s obtained after initiating therapy as stated in the protocol? If so, please provide the ECG details.
8. Please provide the disease status of all the 10 patients with sudden deaths. Were any of the patients in remission?

As you are probably aware, Janet is vacationing beginning today and all of next week so I'm sending the above requests on her behalf.

Thanks--Brenda for Janet

---

Brenda Atkins, Project Manager  
Division of Drug Oncology Products  
Office of New Drugs/Office of Oncology Drug Products

Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Rm. 2122  
Silver Spring, MD 20993  
Phone: 301-796-1324  
Fax: 301-796-9845  
[brenda.atkins@fda.hhs.gov](mailto:brenda.atkins@fda.hhs.gov)

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/s/

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Brenda Atkins  
8/2/2007 05:19:36 PM  
CSO

# TELECONFERENCE MEETING MINUTES

**MEETING DATE:** July 20, 2007 **TIME:** 9:30 am EST

**LOCATION:** FDA White Oak Facility, Conference Room 2201

**NDA: 22-068** Meeting Request Submission Date: July 16, 2007  
Briefing Document Submission Date: N/A

**DRUG:** Tasigna® (nilotinib)

**INDICATION:** Chronic Myelogenous Leukemia, Accelerated Phase (AP) and Chronic Phase (CP), Philadelphia Chromosome Positive

**SPONSOR:** Novartis Pharmaceutical Corporation

**TYPE OF MEETING:** Sponsor requested Telecon to discuss FDA application goal date extension

## **PARTICIPANTS:**

### FDA:

Maitreyee Hazarika, M.D., Medical Reviewer, DDOP  
Robert Kane, M.D., Acting Team Leader, DDOP  
Robert Justice, M.D., Director, DDOP  
Ann Farrell, M.D., Deputy Director, DDOP  
Richard Pazdur, M.D., Director, OODP  
Raji Sridhara, Ph.D., Statistical Team Leader, DDOP  
Janet Jiang, Ph.D., Statistical Reviewer, DDOP  
Qi Liu, Ph.D., Clinical Pharmacology Reviewer, DDOP  
Shwu-Luan Lee, Ph.D., Pharmacology Toxicology Reviewer, DDOP  
John Leighton, Ph.D., Pharmacology Toxicology team leader, DDOP  
Michael Orr, Ph.D., Clinical Pharmacology, Genomics Reviewer DDOP  
Roshni Ramchandani, Ph.D., Clinical Pharmacology QTc Reviewer, DDOP  
Christine Garnett, Pharm. D., QTc Reviewer  
Joe Grillo, Pharm. D., DDMAC  
Janet Jamison, R.N., R.P.M.

### Novartis Pharmaceutical:

Renaud Capdeville, M.D., Clinical (Switzerland)  
Neil Gallagher, M.D., Clinical (Switzerland)  
Chiaki Tanaka, Clinical Pharmacology  
Ming Zheng, Biostatistics  
Ariful Haque, Biostatistics  
Bernd Eschgfäller, Project Management (Switzerland)  
Robert Miranda, Drug Regulatory Affairs

Joseph Quintavalla, Drug Regulatory Affairs  
Prem Narang, Drug Regulatory Affairs

**MEETING OBJECTIVES:** Discuss with the sponsor the agency's concerns and decision to extend the application goal date as communicated to the sponsor by electronic mail July 13, 2007.

**BACKGROUND:** NDA 22-068 application was filed on September 29, 2006 for Tasigna® (nilotinib) for the treatment of chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to at least one prior therapy including Gleevec® (imatinib). On July 13, 2007 the FDA made the decision to extend the goal date by 3 months for this application. Novartis requested the Telecon with FDA on July 16, 2007 to understand more about specific reasons for the extension and how to expedite the continuing FDA review.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

The FDA expressed concern over potential safety issues with Tasigna as reflected in the number of sudden deaths observed on the study and QTc prolongation concerns.. A total of 6 unexplained sudden deaths have been reported out of approximately 750 patients. In the absence of a control arm, these events must be viewed as drug-related.

---

The FDA informed the sponsor that the review of additional data related to the application will continue; however, safety issues will require much further scrutiny.

**DECISIONS REACHED/ACTION ITEMS:**

- The FDA recommended the sponsor request a face to face meeting with the Agency to discuss further the analysis of sudden deaths and related safety events. The sponsor should provide a summary of their analysis for agency review prior to the scheduled meeting.
- The FDA recommended the sponsor contact the Division of Drug Marketing and Advertising and Communication for guidance regarding advertising materials.

The meeting concluded at 10:00 am EST.

Richard Pazdur, M.D. chaired the meeting. Janet Jamison, P.M., facilitated the meeting.

Prepared by:

Janet Jamison, R.N.  
Regulatory Project Manager, DDOP

Concurrence:

Robert Justice, M.D.  
Director, DDOP

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/s/

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Robert Justice  
8/2/2007 03:15:45 PM

## Jamison, Janet

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**From:** Jamison, Janet  
**Sent:** Tuesday, July 31, 2007 6:45 AM  
**To:** robert.miranda@novartis.com; 'joseph.quintavalla@novartis.com'  
**Subject:** N22068 FDA Request for Information-Protocol 2101

Hi Bob,

See the request below from the reviewers:  
Please send a copy of the current version of protocol 2101.

Let me know if you have any questions.

Janet

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2165  
Silver Spring, MD 20993  
301-796-2313  
FAX 301-796-9845  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
7/31/2007 06:49:32 AM  
CSO

**Jamison, Janet**

---

**From:** Jamison, Janet  
**Sent:** Monday, July 30, 2007 8:36 AM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22068 - Request to review rationale- denominator-CML-CP efficacy analysis-FDA Response

Bob,  
In reference to your July 18, 2007 request, see the reviewers response below:

We have determined that these patients should not be excluded from the denominator. Although a sensitivity analysis can be done, this is the most appropriate estimate which will be used for labeling. This also reflects the use of bone marrow cytogenetics as the standard method which has also been used for other drugs.

Please let me know if you have any questions.

Janet Jamison

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2165  
Silver Spring, MD 20993  
301-796-2313  
FAX 301-796-9845  
E-Mail: janet.jamison@fda.hhs.gov

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**From:** robert.miranda@novartis.com [mailto:robert.miranda@novartis.com]  
**Sent:** Wednesday, July 18, 2007 4:58 PM  
**To:** Jamison, Janet  
**Subject:** Re: N22068 - Request to review rationale for denominator in CML-CP efficacy analysis

Dear Janet,

Based on the Division's recommendations and its concerns with the use and validity of FISH we excluded these patients from the numerator, however we believe that it is also correct to exclude these from the denominator. Please see attached document for a discussion of our rationale.

We appreciate the Division's consideration regarding this topic.

Thank you,  
Bob

.....  
**Robert A. Miranda**  
Senior Director

7/30/2007

**Drug Regulatory Affairs**

**Oncology Business Unit**

Building 104/ Room 2G37

Novartis Pharmaceuticals

One Health Plaza

East Hanover, New Jersey 07936

**Phone:** 862-778-2282

**Fax:** 973-781-5217

**E-mail:** [Robert.Miranda@Novartis.com](mailto:Robert.Miranda@Novartis.com)

**Assistant:** Diana Arteaga +1 (862) 778-8784

\*\*\*\*\*

**Exclusion of CML-CP patients who fail to satisfy major entry criteria**

Novartis is cognizant of the discussion with the Division on June 22, 2007, and its concerns with the use and validity of FISH in the regulatory setting as it pertains to assessing response rate as the endpoint for this NDA application. Novartis believes that forty-eight (N=48) patients in whom entry criteria were not considered adequate by the Division need to be excluded from both the denominator and numerator in the calculation of the treatment effect. Thus the total sample size of 280 should be reduced to 232". This is methodologically correct given the general framework noted in section 5.2.1 of the ICH E9 entitled "Statistical Principles for Clinical Trials (final September 1998), which states:

*"There are a limited number of circumstances that might lead to excluding randomized subjects from the full analysis set, including the failure to satisfy major entry criteria.....". "Subjects who fail to satisfy an entry criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:*

- a. The entry criterion was measured prior to randomization.*
- b. The detection of the relevant eligibility violations can be made completely objectively".*
- c. All subjects receive equal scrutiny for eligibility violations".*
- d. All detected violations of the entry criteria are excluded."*

This excerpt (and all its elements) clearly supports our position to exclude those patients (i.e. "...who did not meet major entry criteria..."). To minimize bias, it is not sufficient just to consider patients in the numerator as non-responders alone but the removal of such patients in the denominator is necessary to characterize the effect in an unbiased manner. These exclusions are justified for this dataset even though the trial design is 'open-label'

Therefore, we propose that in the efficacy analysis for CML-CP patients the total sample size should be limited to only patients who met the critical entry criteria as proposed by the Division (N = 232).

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/s/

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Janet Jamison  
7/30/2007 08:43:49 AM  
CSO

## Jamison, Janet

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**From:** Jamison, Janet  
**Sent:** Friday, July 20, 2007 2:17 PM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22068-FDA Request for Information-AE Summary Data 7-20-07

Hi Bob,

Please see the request below from the reviewers:

Please provide a consolidated summary and the Case Report Forms and narratives of the following adverse events in the phase 1/2 clinical trial with Tasigna:

- syncope (include AE MedDRA preferred terms including 'syncope' terms and 'loss of consciousness')
- seizures
- ventricular tachycardia (include 'supraventricular tachycardia', 'tachycardia' and 'tachyarrhythmia')
- torsade de pointes

Please also include the number and Case Report Forms and narratives of patients withdrawn from study due to an adverse event.

It is recognized that this information is contained within the data previously submitted for this application. However, in the interest of time and to efficiently proceed with a safety determination, we are requesting the sponsor to summarize this data and include Case Report Forms and narratives all in one submission package to N22-068.

If you have any questions, please let me know.

Janet

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2165  
Silver Spring, MD 20993  
301-796-2313  
FAX 301-796-9845  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
7/20/2007 02:20:55 PM  
CSO

## Jamison, Janet

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**From:** Jamison, Janet  
**Sent:** Thursday, July 19, 2007 10:33 AM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22068 FDA Request for Information 7-19-07

Bob,

Please see request below from reviewers:

Please provide the total number of patients treated on the early access protocol.

Janet

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2165  
Silver Spring, MD 20993  
301-796-2313  
FAX 301-796-9845  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
7/19/2007 10:41:48 AM  
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**Jamison, Janet**

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**From:** Jamison, Janet  
**Sent:** Wednesday, July 18, 2007 11:05 AM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22068-FDA Request for SD Clarification 7-18-07

Bob,  
See the request from reviewers below:

Please clarify why patient 501\_3002 is not counted as a sudden death. He died at home on day 27.

Janet

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2165  
Silver Spring, MD 20993  
301-796-2313  
FAX 301-796-9845  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
7/18/2007 11:09:03 AM  
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## REQUEST FOR CONSULTATION

TO (Office/Division): Division of Cardio Renal Products, ODE-1, Attn. Devi Kozelli, Regulatory Project Manager

FROM (Name, Office/Division, and Phone Number of Requestor): Janet Jamison, PM/DDOP/796-2313/HFD-150

DATE  
8-16-07

IND NO.

NDA NO.  
22-068

TYPE OF DOCUMENT  
Urgent- Cardiology  
Review of Sudden  
Deaths/QTc prolongation

DATE OF DOCUMENT  
7-16-07

NAME OF DRUG  
Tasigna (nilotinib)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
8-6-07

NAME OF FIRM: Novartis

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** Urgent Request- Cardiology Consult: Please evaluate the sudden deaths observed for Tasigna (total of n=10) across all studies to date, and possible cardiac risk to include association with known QTc prolongation. Attached are the recent FDA-sponsor communications and links to the relevant datasets. The Division is considering convening an AC which will include Cardiology for this application (PDUFA Goal Date extended until October 29, 2007). Please contact me or Maitreyee Hazarika, Medical Officer, if additional information is needed. Consult also sent to IRT-QT on July 16, 2007.

SIGNATURE OF REQUESTOR  
Janet Jamison, PM

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Janet Jamison  
7/18/2007 03:18:10 PM

## Jamison, Janet

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**From:** Jamison, Janet  
**Sent:** Tuesday, July 17, 2007 10:01 AM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22068 FDA Request for Information 7-17

Bob,  
See the request below from the reviewers:

Please clarify the precautions in the early access/treatment protocol regarding the use of CYP inhibitors and concomitant medications that prolong QT interval.

Janet

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
FAX 301-796-9845  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
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**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

DATE: July 16, 2007

TO: Janet Jamison, Regulatory Project Manager  
Maitreyee Hazarika, M.D., Reviewing Medical Officer  
Division of Oncology Drug Products, HFD-150

THROUGH: Leslie K. Ball, M.D.  
Branch Chief  
Good Clinical Practice Branch 2, HFD-47  
Division of Scientific Investigations

FROM: Bob Young

SUBJECT: Evaluation of Sponsor and Clinical Inspections

NDA: 22-068

NME: Yes

APPLICANT: Novartis Pharmaceuticals Corporation  
East Hanover, NJ

DRUG: nilotinib (Tasigna<sup>(R)</sup>) New Molecular Entity

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment ████████ of Chronic Phase (CP) and accelerated phase (AP) Philadelphia chromosome positive Chronic Myelogenous leukemia (CML) in adult patients resistant to or intolerant to ████████ prior therapy including Gleevec (imatinib).

PROTOCOL: 2101(E2 and E3) - A phase IA/II multicenter, dose-escalation study of oral AMN 107 on a continuous daily dosing schedule in adult patients with Gleevec resistant CML in accelerated phase or blast crisis, relapsed/refractory Ph+ALL, and other hematologic malignancies.

DOSAGE FORM AND ROUTE OF ADMINISTRATION: Tasigna (nilotinib) 200mg Capsule for oral administration.

CONSULTATION REQUEST DATES: 12/12/2006 and 05/18/2007

DIVISION ACTION GOAL DATE: July 13, 2007

PDUFA DATE: July 27, 2007

## I. BACKGROUND:

The clinical investigator inspections were routine inspections including review of records for the primary efficacy endpoint, eligibility for the study, and toxicity. Site inspections outside the US were assigned because there was insufficient domestic data. All assigned sites enrolled larger number of subjects and had a high number of treatment responders.

The sponsor inspection was a directed inspection. The sponsor on May 16, 2007 informed the reviewing division that it was being sued in NJ state court by one of its former managers. After being served the sponsor provided FDA a copy of the complaint and a response by the sponsor. The sponsor assured FDA it had audited its data base both internally and by way of an external independent reviewer.

On June 28, 2007 at FDA's NJ District Office, the informant, David Olagunju, was jointly interviewed by FDA field and headquarters. On July 9, 2007 a sponsor inspection was initiated with headquarters participation. The purpose of the inspection was to verify that the sponsor had and was following proper procedures for data handling and analysis, and had in fact responsibly audited the data base submitted after Olagunju complained. No substantial deviations were found and no conditions were found for inclusion on a 483. A headquarters' biostatistician participated in the Olagunju interview and sponsor inspection.

A program sponsor/monitor inspection is ongoing at the time of this CIS.

## II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Country	Insp. Date	EIR Received Date	Final Classification
J. Pinilla-Ibarz (502)	Tampa, FL		26 Mar 07	25 Apr 07	Pending
H. Kantarjian (501)	Houston, TX		14 Mar 07	4 Apr 07	Pending
P. LeCoutre (304)	Berlin	Germany	16 Apr 07	Pending	Pending
Ottman & Wolfgang	Frankfurt	Germany	16 Apr 07	Pending	Pending
Novartis	E. Hanover NJ		9 Jul 07	Pending	Pending

### Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

### A. Clinical Sites:

1. Javier Pinilla-Ibarz, M.D., Ph.D.  
Tampa, FL.  
Site 502

Successor clinical investigator to:

\_\_\_\_\_

a. What was inspected: 24 subjects were entered into the study and the records of 9 subjects were audited.

b. Limitations of inspection: none

c. General observations/commentary: No significant discrepancies or deviations were encountered and no 483 was issued. Field classification was NAI.

d. Assessment of data integrity: data from this site is acceptable for consideration in the NDA review decision.

2. Hagop Kantarjian, M.D.  
Houston, TX  
Site 501

a. What was inspected: 46 subjects were entered and the records of 15 subjects were audited.

b. Limitations of inspection: none

c. General observations/commentary: No notable objectionable conditions were found and no 483 was issued.

d. Assessment of data integrity: The data at this site is acceptable for consideration in the NDA review decision.

3. Philipp Le Coutre, M.D.  
Berlin, Germany  
Site 304

The EIR has not yet been received.

a. What was inspected: pending

b. Limitations of inspection: pending

c. General observations/commentary: The field investigator has advised DSI that he found no problems at the site and issued no 483.

Observations noted above are based on communications from field investigator, and an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR

d. Assessment of data integrity: The data from this site is acceptable for consideration in the NDA review decision.

4. Oliver G. Ottman, M.D.  
Johann Wolfgang, M.D.  
Frankfurt, Germany  
Site 301

The EIR has not yet been received.

a. What was inspected: pending

b. Limitations of inspection: pending

c. General observations/commentary: The field investigator has advised DSI that he found no problems at the site and issued no 483.

Observations noted above are based on communications from field investigator, and an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR

d. Assessment of data integrity: The data from this site is acceptable for consideration in the NDA review decision.

B. Sponsor

Novartis Pharmaceuticals Corporation  
East Hanover, NJ

An EIR has not yet been received. The inspection is still on going and has not closed.

a. What was inspected: pending

b. Limitations of inspection: none

c. General observations/commentary: It appears that there are no substantial deviations.

Observations noted above are based on participation in the inspection and communications from field investigator, an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR

d. Assessment of data integrity: The data submitted can be used for consideration in the NDA review decision.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

No significant problems were found at the clinical site or at the sponsor.

Follow-up actions to be taken, if any: none.

Observations noted above are based on a preliminary review of the available EIRs, communications from field investigators, and participation in the sponsor inspection. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

*{See appended electronic signature page}*

Bob Young

CONCURRENCE:

Supervisory comments

*{See appended electronic signature page}*

Leslie K. Ball, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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/s/

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Yolanda Patague  
7/17/2007 09:55:49 AM  
SECRETARY

Leslie Ball  
7/17/2007 10:09:42 AM  
MEDICAL OFFICER

## REQUEST FOR CONSULTATION

TO (Office/Division): Denise Hinton/Interdisciplinary Review Team for QT Studies, Devi Kozelli, PM

FROM (Name, Office/Division, and Phone Number of Requestor): Janet Jamison, PM/DDOP/796-2313/HFD-150

DATE  
7-16-07

IND NO.

NDA NO.  
22-068

TYPE OF DOCUMENT  
Urgent- Review of Sudden Deaths/QTc prolongation

DATE OF DOCUMENT  
7-16-07

NAME OF DRUG  
Tasigna (nilotinib)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
8-6-07

NAME OF FIRM: Novartis

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** Urgent request: Please evaluate the sudden deaths observed for Tasigna (total of n=10) across all studies to date, and possible association with QT prolongation. Attached are the relevant FDA-sponsor communications and links to the relevant datasets. The application goal date has been extended until October 29, 2007. Please contact me or Maitreyee Hazariks, Medical Officer if additional information is needed.

SIGNATURE OF REQUESTOR  
Janet Jamison, PM

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

-----  
Janet Jamison

7/16/2007 01:33:25 PM

## Jamison, Janet

---

**From:** Jamison, Janet  
**Sent:** Monday, July 16, 2007 1:03 PM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22068 FDA Request for I69764 Cardiac Monitoring Information

Bob, see information request from the reviewers below:

Given the sudden deaths observed in the early access/treatment protocol, please clarify the current ECG monitoring and other cardiac monitoring in the early access/treatment protocol.

Janet

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
FAX 301-796-9845  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

-----  
Janet Jamison  
7/16/2007 01:05:43 PM  
CSO



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-068

Novartis Pharmaceuticals Corporation  
Attention: Robert A. Miranda  
One Health Plaza, Building 105/2W200  
East Hanover, NJ 07936-1080

Dear Mr. Miranda:

Please refer to your September 29, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tassigna (nilotinib) oral capsules.

On May 10, June 15, June 25, and July 2, 2007 we received your amendments to this application. We consider the aggregate of these amendments to be a major amendment. Therefore, we are extending the goal date by three months to provide time for a full review of these submissions. The extended user fee goal date is October 29, 2007.

If you have any questions, please call Janet Jamison, Project Manager, at 301-796-2313.

Sincerely,

*{See appended electronic signature page}*

Frank Cross, Jr.  
Chief, Project Management Staff  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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/s/

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Frank Cross

7/13/2007 03:43:57 PM

## Jamison, Janet

---

**From:** Jamison, Janet  
**Sent:** Thursday, July 12, 2007 11:55 AM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22068-FDA Request for Information [REDACTED]

**Importance:** High

Bob,  
Please see the request below:

1. In reference to your proposed amendment to the [REDACTED] to drop the AMN107 (nilotinib) arm, we note your rationale that mentions 6 sudden deaths occurring in clinical trials of AMN107.
  - a. Please clarify whether these deaths were previously reported to the FDA and whether they are in addition to the seven included in the NDA application (nilotinib).
  - b. Please provide trials and patient identification numbers of all sudden deaths on patients being treated on AMN107.
  - c. If these deaths were previously reported to the FDA and known to Novartis in 2006, why is the [REDACTED] study only now being amended to drop the AMN107 arm?
  - d. You have previously submitted additional proposed clinical trials examining the role of AMN107 in newly diagnosed CML-CP. Are you planning on initiating these trials in light of your decision to amend the [REDACTED] study?

Please provide answers to these questions by close of business today. Pending the answers to the above questions the FDA may require a teleconference with you on Friday.

Janet

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
FAX 301-796-9845  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
7/12/2007 12:01:49 PM  
CSO

**Jamison, Janet**

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**From:** Jamison, Janet  
**Sent:** Friday, June 29, 2007 11:32 AM  
**To:** 'joseph.quintavalla@novartis.com'  
**Cc:** robert.miranda@novartis.com  
**Subject:** NDA 22-068 Follow-up June 22 TC- FDA Response

Joe, Bob,

The Division would like for you to focus on the revised FDA Efficacy Responses, CML-CP, sent by e-mail transmission June 26 and the revised FDA Efficacy Responses, CML-AP, sent by e-mail transmission June 27 for the Tasigna labeling content. The revised FDA responses did take into account the Telecon discussions.

Please acknowledge receipt. Let me know if you have any questions.

Janet

---

**From:** joseph.quintavalla@novartis.com [mailto:joseph.quintavalla@novartis.com]  
**Sent:** Thursday, June 28, 2007 1:23 PM  
**To:** Jamison, Janet  
**Cc:** robert.miranda@novartis.com  
**Subject:** AMN107 NDA 22-068 Follow-up June 22 TC

Dear Janet,

Following the AMN107 teleconference on June 22, 2007, Novartis has revisited the data from our submission. Attached is our analysis of the information and response criteria as we had agreed. Please forward this to your team for consideration.

Best regards,

Joe

6/29/2007

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/s/

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Janet Jamison  
6/29/2007 11:39:03 AM  
CSO

## Jamison, Janet

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**From:** Jamison, Janet  
**Sent:** Wednesday, June 20, 2007 9:16 AM  
**To:** 'robert.miranda@novartis.com'  
**Cc:** joseph.quintavalla@novartis.com  
**Subject:** N22068-FDA Request for Pharmacology Datasets

Bob,  
See request below:

Please submit a dataset for the 111 patients that have the UGT1A1 genotype (6/6), (6/7), and (7/7) from study CAMN107A2101-03. For each patient, please include the total bilirubin values (micro mol/L), ALT values, AST values and ALP levels.

Janet

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
FAX 301-796-9845  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
6/21/2007 10:55:48 AM  
CSO

## Jamison, Janet

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**From:** Jamison, Janet  
**Sent:** Tuesday, June 19, 2007 12:12 PM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22068-FDA Request for Pharmacology Information

Bob,

Can you confirm the studies below are still being conducted for Tasigna as presented by Novartis in November?  
If yes, what is the current status/projected completion date for each study?

Ongoing and planned Clin Pharm studies:

- 1) Nilotinib pharmacokinetics in subjects with hepatic impairment (3Q 2007).
- 2) Absolute bioavailability study in healthy subjects (4Q 2007).

Janet

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
FAX 301-796-9845  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
6/21/2007 11:01:08 AM  
CSO

## Jamison, Janet

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**From:** Jamison, Janet  
**Sent:** Monday, June 11, 2007 6:54 AM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22068-FDA Request for Information

Bob, the reviewers have requested the following information from the Tasigna application review:

1. The 120 day updated safety study report states that there are 318 patients in CML-CP and 120 patients in CML-AP safety population. The updated datasets submitted contain data on 280 patients for CML-CP and 104 patients for CML-AP patients. Please explain this discrepancy.
2. For patient #0202\_04002, there is a grade 2 adverse event (AE) noted without the SOC term and PT term description. The AE name is "prolonged QTC". Please explain why this AE was not coded and therefore not included in the AE dataset.
3. Please submit Case Report Forms for the following patients:  
0304\_04003 (check why one blank AE)  
0602\_04002  
0702\_04004  
0306\_03001 (check that no AEs)

Please acknowledge receipt and send any responses as available to me.

Janet Jamison

Project Manager  
FDA/CDER/ODDP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
6/11/2007 06:59:02 AM  
CSO

**Jamison, Janet**

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**From:** Jamison, Janet  
**Sent:** Tuesday, May 29, 2007 11:59 AM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22068-FDA Medication Guide Clarification

Bob,  
Yes, the agency's request is to convert the current Patient Information section into a Medication Guide (MG).

A Medication Guide always replaces a Patient Information Sheet. A product can only have one approved patient labeling and a MG supersedes any other patient labeling.

Let me know if you have any other questions.

Janet

---

**From:** robert.miranda@novartis.com [mailto:robert.miranda@novartis.com]  
**Sent:** Friday, May 25, 2007 3:15 PM  
**To:** Jamison, Janet  
**Subject:** Re: N22068-FDA Request-Risk Management Plan Proposal

Hi Janet,

As you know, in the most recent updated PI we sent to the NDA on 5/3/07 to include the updated 120-day data, we also included a new "Patient Information" section similar to what Sprycel did (see attached) . Do you want us to convert our Patient Information section into a "Medication Guide" following the CRF cited instead?

Thanks  
Bob.....

"Jamison, Janet" <Janet.Jamison@fda.hhs.gov>

05/25/2007 02:09 PM

To: robert.miranda@novartis.com  
cc:  
Subject: N22068-FDA Request-Risk Management Plan Proposal

Bob,

Following review of your Risk Management Plan for nilotinib (Tasigna), the Agency has determined that a Medication Guide is required for patient labeling consistent with 21CFR208 due to the following circumstances related to the serious adverse event of QT prolongation,

5/29/2007

drug interactions and directions for use related to food intake.

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Please let me know if you have any questions.

Regards,

Janet Jamison

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
E-Mail: [janet.jamison@fda.hhs.gov](mailto:janet.jamison@fda.hhs.gov)

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/s/

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Janet Jamison  
5/29/2007 12:04:06 PM  
CSO

## Jamison, Janet

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**From:** Jamison, Janet  
**Sent:** Tuesday, May 22, 2007 1:28 PM  
**To:** robert.miranda@novartis.com  
**Subject:** N22068 FDA Request for Information

Bob,

The reviewers have requested the following information from the March submission data:

1. Please explain how patient # 0502\_04012 appears in both the initial and additional populations in the updated datasets.
2. Please state the version of MedDRA used to code adverse events.

Janet

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
5/23/2007 10:56:50 AM  
CSO

## REQUEST FOR CONSULTATION

TO (Office/Division): Denise Hinton/Interdisciplinary Review Team for QT Studies

FROM (Name, Office/Division, and Phone Number of Requestor): Janet Jamison, PM/DDOP/796-2313/HFD-150

DATE  
5-14-07

IND NO.

NDA NO.  
22-068

TYPE OF DOCUMENT  
Final Study Report-BZ

DATE OF DOCUMENT  
5-10-07

NAME OF DRUG  
Tasigna (nilotinib)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
06/29/07

NAME OF FIRM: Novartis

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Consult requested for QT review of Final Study Report for 2115: Safety/PK healthy volunteers for any relevant safety QT issues. Minor Amendment available in EDR:\CDSESUB1\N22068\N\_000\2007-05-10  
DDOP team labeling meetings are scheduled to begin June 7, 2007. MO: M. Hazarika. PDUFA Due Date is 7-29-07

SIGNATURE OF REQUESTOR  
Janet Jamison, PM

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Janet Jamison  
5/16/2007 01:52:46 PM

## Jamison, Janet

---

**From:** Jamison, Janet  
**Sent:** Wednesday, April 25, 2007 2:40 PM  
**To:** 'robert.miranda@novartis.com'  
**Cc:** Cross Jr, Frank H  
**Subject:** N22068-FDA Request for Information

Bob, please see the reviewer request below for the Tasigna N22068 application:

1. Please describe your method for deriving the safety dataset (p1safety.xpt and p2safety.xpt, submitted in 16-Feb-2007) for the population PK/PD analysis. In particular, please describe the method you used to calculate the normalized values for total bilirubin and lipase (normalized by the lab's upper and lower normal range limits). Please indicate if there is any exclusion rules used to derive these datasets.
2. In Table 4-1 from your population PK/PD Modeling report (Submitted in 16-Feb-2007), it is indicated that PK data from 35 AP patients and 92 CP patients in Phase II were used in your population PK analysis. However, it appears to the FDA reviewer PK data from 43 AP patients and 167 CP patients in Phase II were used in your population PK analysis. Please double check and confirm these numbers.

I will be out of town until next Thursday. If you are prepared to respond before that time copy Frank Cross on the message. He will make sure the response gets to the reviewer in my absence.

Regards,  
Janet Jamison

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
5/4/2007 02:13:10 PM  
CSO

## Jamison, Janet

---

**From:** Jamison, Janet  
**Sent:** Thursday, April 12, 2007 1:25 PM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22068 FDA Request for Clinical Information

Bob,  
The Tassigna clinical reviewers have requested the following:

1. In SCS Tables 5-1 and 5-5, please explain why you have removed patients from the denominator. It is generally not acceptable.
2. In the datasets LRS, please explain the grading of zero and minus 1, 2, 3 and 4 recorded in the CTC\_1C column.
3. Please clarify that only laboratory abnormalities that required a medical intervention were reported as an adverse event (AE) and these AEs appear in the AEV dataset.

Janet Jamison

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
4/12/2007 01:28:44 PM  
CSO

**Jamison, Janet**

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**From:** robert.miranda@novartis.com  
**Sent:** Wednesday, April 04, 2007 6:21 PM  
**To:** Jamison, Janet  
**Subject:** Re: N22-068 FDA Request for Information-Labeling  
**Attachments:** emfalert.txt

Hi Janet,

In the original NDA, the Summary of Clinical Safety (SCS) database was used to derive the data presented in Table 3 of the PI. This consists of CML-CP (2101E2) with 282 patients and CML-AP (2101E1) with 89 patients. Please refer to SCS in-text tables 5-1, 5-5 and 11-1.

Please let me know if you have any questions or need further clarification.

Thanks  
Bob.....

\*\*\*\*\*

**Robert A. Miranda**  
**Senior Director**  
**Drug Regulatory Affairs**  
**Oncology Business Unit**  
Building 104/ Room 2G37  
Novartis Pharmaceuticals  
One Health Plaza  
East Hanover, New Jersey 07936  
**Phone:** 862-778-2282  
**Fax:** 973-781-5217  
**E-mail:** [Robert.Miranda@Novartis.com](mailto:Robert.Miranda@Novartis.com)  
**Assistant:** Diana Arteaga +1 (862) 778-8784  
\*\*\*\*\*

"Jamison, Janet" <[Janet.Jamison@fda.hhs.gov](mailto:Janet.Jamison@fda.hhs.gov)>

04/04/2007 07:23 AM

To: robert.miranda@novartis.com  
cc:  
Subject: N22-068 FDA Request for Information-Labeling

Hi Bob,

The reviewers have requested the following information:

1. Please clarify which dataset was used to derive the values shown in Table 3 of the Tassigna label.

4/5/2007

Regards,  
Janet Jamison

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
E-Mail: [janet.jamison@fda.hhs.gov](mailto:janet.jamison@fda.hhs.gov)

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/s/

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Janet Jamison  
4/5/2007 07:27:09 AM  
CSO

**Jamison, Janet**

---

**From:** Jamison, Janet  
**Sent:** Friday, March 09, 2007 7:00 AM  
**To:** 'robert.miranda@novartis.com'  
**Cc:** 'joseph.quintavalla@novartis.com'  
**Subject:** RE: N22068 Tasigna- FDA Request for Information (Clarification to Question #3)

Bob,  
In response to question 3 Class Specific Adverse Events, the reviewers request the following:

Please look into the following at the very least:  
Fluid retention and edema  
Congestive heart failure  
Hemorrhage (including GI and CNS)  
Myelosuppression  
Hepatotoxicity  
QT prolongation  
Pancreatitis  
Hypophosphatemia, with associated changes in bone and mineral metabolism

Let me know if you have further questions.

Janet Jamison

---

**From:** robert.miranda@novartis.com [mailto:robert.miranda@novartis.com]  
**Sent:** Tuesday, March 06, 2007 10:18 AM  
**To:** Jamison, Janet  
**Subject:** RE: N22068 Tasigna- FDA Request for Information (Clarification to Question #3)

Hi Janet,

Sorry to bother you but any success in getting some clarification to this pending question? We are proceeding to prepare an answer but we want to make sure we address all the concerns by the reviewer. I expect to provide this answer with the requested datasets by end of this week.

For your information, there is a Novartis global DRA meeting in Florida next week. I have a blackberry so I can monitor the emails. Of course you can also reach me by phone if needed.

Thanks  
Bob.....

"Jamison, Janet"  
<Janet.Jamison@fda.hhs.gov>

To: robert.miranda@novartis.com  
cc:  
Subject: RE: N22068 Tasigna- FDA Request for Information (Clarification to Question #3)

02/28/2007 08:19 AM

#3)

3/9/2007

I will inquire with the reviewer.

Janet

---

**From:** robert.miranda@novartis.com [mailto:robert.miranda@novartis.com]  
**Sent:** Wednesday, February 28, 2007 7:53 AM  
**To:** Jamison, Janet  
**Subject:** Re: N22068 Tasigna- FDA Request for Information (Clarification to Question #3)

Hi Janet,

Regarding Question #3 below, can you specify any AEs you want us to include which the reviewer considers a "class-specific adverse event"? We have certain AEs in mind (e.g. fluid retention) but we want to make sure we address at least the ones you are most interested in.

Any input would be very helpful.

Thanks  
Bob.....

\*\*\*\*\*

**Robert A. Miranda**  
**Director**  
**Drug Regulatory Affairs**  
**Oncology Business Unit**  
 Building 104/ Room 2G37  
 Novartis Pharmaceuticals  
 One Health Plaza  
 East Hanover, New Jersey 07936  
**Phone:** 862-778-2282  
**Fax:** 973-781-5217  
**E-mail:** Robert.Miranda@Novartis.com  
**Assistant:** Diana Arteaga +1 (862) 778-8784

\*\*\*\*\*

"Jamison, Janet" <Janet.Jamison@fda.hhs.gov>

02/22/2007 01:51 PM

To: robert.miranda@novartis.com  
 cc:  
 Subject: N22068 Tasigna- FDA Request for Information and T-Con

Bob,

Two requests:

A. The reviewers have requested a response to the information below related to the Tasigna application.

B. Is appropriate Novartis staff available for a 30 minutes T-Con with the Medical Reviewer and Team Leader to discuss questions # 1 and 2?

I have tentatively reserved next Wednesday February 28 from 10:30 am until 11 am

3/9/2007

FDA Request for Information:

1. To re-phrase previous question 5, please explain how the HR was "calculated". If an algorithm was used, state where this is provided in the protocol or in the NDA submission.
2. Please explain what you mean by "electronic" capture of laboratory data.
3. Please explore and discuss the safety profile with regard to class-specific adverse events.
4. Please submit the datasets for the updated safety and efficacy data.

Let me know if Wednesday morning will work for you.

Regards,

Janet Jamison

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
E-Mail: [janet.jamison@fda.hhs.gov](mailto:janet.jamison@fda.hhs.gov)

3/9/2007

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/s/

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Janet Jamison  
3/9/2007 09:51:52 AM  
CSO

## Jamison, Janet

---

**From:** Jamison, Janet  
**Sent:** Friday, February 23, 2007 12:40 PM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** N22068 FDA Request for Clinical Information 2-23-07

Hi Bob,

See attached request for information from the reviewers:

1. Patient #0304\_04008 has a decrease in cells positive for chromosome in the BM from 27 to 25. Please explain why you have considered this patient to have a partial response?
2. Patient #0502\_04012 had no change in the number of cells positive for chromosome in the BM and FISH increased from 10 to 74. Please explain why you have considered this patient to have a partial response?
3. Patient #0501\_04002 had no change in the bone marrow response and FISH remained zero throughout. Please explain why you have considered this patient to have a complete response?
4. Patient #0702\_04003 had an increase in the cells positive for chromosome in the BM and has one FISH positive in 34 cells. Please explain why you have considered this patient to have a partial response?
5. Please explain how you have adjudicated responses when BM has shown zero cells positive for chromosome but FISH has shown cells positive for Ph chromosome.

Janet Jamison

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
2/23/2007 12:43:18 PM  
CSO

**Jamison, Janet**

---

**From:** robert.miranda@novartis.com  
**Sent:** Tuesday, February 13, 2007 2:23 PM  
**To:** Jamison, Janet  
**Subject:** Re: N22068 Application-FDA Request for Information - RESPONSE  
**Attachments:** emfalert.txt

Dear Janet,

The quoted statement in our letter of January 3, 2007 concerning additional concentration -QT analysis including "models relating delays in maximum concentration, maximum response and Emax model relating concentration" was incorrect. Although requested, these were not conducted and our rationale is explained below. We apologize for this miss-communication.

An "interim" report for the QT Study 2119 was included in our original NDA filed on September 29, 2006. The study report included an exploratory analyses to characterize the relationship of nilotinib serum concentrations to changes in cardiac conduction intervals (primarily QTcF). The population slope ( $\beta$ ) and standard error of slope (SE) of the nilotinib serum concentration and  $\Delta$ QTcF (baseline- adjusted QTc) were estimated using a linear random effects model fitting for terms, baseline QTcF, nilotinib serum concentration and subject, where the subject was considered as a random factor. The above analyses considered the change from baseline in QTcF unadjusted for placebo effects ( $\Delta$ QTcF).

According to the FDA request on Sept 12, 2006 (Type A Meeting: F/U to QT Study), the above exploratory analyses were repeated for  $\Delta\Delta$ QTcF, change from baseline in QTcF (-placebo AND -baseline adjusted). The mean maximum effect and upper one-sided 95% confidence limit were computed from the mean maximum nilotinib serum concentration ( $\bar{C}_{max}$ ) in each cohort using a linear mixed effects model using the following equations:

$$\text{Mean Max Effect} : \bar{C}_{max} \cdot \beta$$

$$\text{Upper 95\% CI} : \bar{C}_{max} \cdot \beta + (z_{0.05} \cdot SE_{\beta} \cdot \bar{C}_{max})$$

The results from the above  $\Delta$ QTcF and DDQTcF analyses were provided in the final report submitted on January 3, 2007.

The  $\Delta\Delta$ QTcF profile on Day 3 increased with the nilotinib serum concentration in parallel immediately following post-dose and reached values similar to baseline values at 48-72 hours post-dose, where nilotinib concentrations were sufficiently low (e.g., >100 ng/mL at 72 hours post-dose). The increase in  $\Delta\Delta$ QTcF mirrored the increase in serum concentrations and therefore, did not suggest a need for a delayed response model.

A graphical display of data and other exploratory analyses suggested that a linear relationship between the DDQTcF and serum concentration were more appropriate than a nonlinear relationship such as Emax. Also, there were no evidence of DDQTcF plateauing at higher concentrations. These led to a decision not to explore Emax model in our analyses. Our understanding is that the linear model provides a better fit and a conservative estimate for the upper one-sided 95% confidence limit for the range of concentrations observed.

Please let me know if you have any further questions or comments.

Thanks,

2/15/2007

Bob

\*\*\*\*\*  
**Robert A. Miranda**  
**Director**  
**Drug Regulatory Affairs**  
**Oncology Business Unit**  
Building 104/ Room 2G37  
Novartis Pharmaceuticals  
One Health Plaza  
East Hanover, New Jersey 07936  
**Phone:** 862-778-2282  
**Fax:** 973-781-5217  
**E-mail:** [Robert.Miranda@Novartis.com](mailto:Robert.Miranda@Novartis.com)  
**Assistant:** Diana Arteaga +1 (862) 778-8784  
\*\*\*\*\*

"Jamison, Janet" <[Janet.Jamison@fda.hhs.gov](mailto:Janet.Jamison@fda.hhs.gov)>

To: [robert.miranda@novartis.com](mailto:robert.miranda@novartis.com)  
cc:  
Subject: N22068 Application-FDA Request for Information

02/06/2007 02:50 PM

Bob,

The reviewers have requested the following information:

We are seeking clarification regarding the concentration-QT analysis conducted for study 2119. The cover letter accompanying the final clinical study report (dated 3-Jan-2007) indicated that additional concentration-QT analysis including "models relating delays in maximum concentration, maximum response and Emax model relating concentration" had been conducted. However there was no description or results of the analysis in the study report for study 2119.

Upon our request on 12-Jan-2007, we received (on 19-Jan-2007) the datasets for the concentration-QT analysis and two SAS program files for the estimation of changes in QTcF at Cmax (table 11-12 in the clinical study report). There were no analysis or program files for the additional analysis mentioned in the 3-Jan-2007 cover letter.

- 1) Please clarify if the additional analyses mentioned in your cover letter of 3-Jan-2007 were, in fact, conducted, for study 2119.
- 2) If so, please submit a summary of the methods and results, as well as the analysis files (datasets and program files), for the additional analyses (models relating delays in maximum concentration, maximum response and Emax model relating concentration).

Regards,  
Janet Jamison

2/15/2007

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
E-Mail: [janet.jamison@fda.hhs.gov](mailto:janet.jamison@fda.hhs.gov)

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/s/

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Janet Jamison  
2/15/2007 08:09:36 AM  
CSO

**Jamison, Janet**

---

**From:** Jamison, Janet  
**Sent:** Tuesday, February 06, 2007 12:37 PM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** Correction N22068 1-12-07 Meeting Minutes- FDA Attendee

Bob,

For your Tassigna files, the statistical reviewer was incorrectly listed in the January 12, 2007 90 Day Status Update Conference FDA Meeting Minutes.

The FDA participant was Xiaoping Jiang, Statistical Reviewer  
Chia-wen Ko, Statistical Reviewer was not in attendance.

My apologies for the confusion. Please add this addendum to your file.

Janet Jamison

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
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# TELECONFERENCE MEETING MINUTES

**MEETING DATE:** January 12, 2007 **TIME:** 1:00 pm EST

**LOCATION:** FDA White Oak Facility, Conference Room 2201

**NDA: 22-068** Meeting Request Submission Date: September 29, 2006  
Briefing Document Submission Date: N/A

**DRUG:** Tasigna® (nilotinib)

**INDICATION:** Chronic Myelogenous Leukemia, Accelerated Phase (AP) and Chronic Phase (CP)

**SPONSOR:** Novartis Pharmaceutical Corporation

**TYPE OF MEETING:** 90 Day Post NDA Submission Conference

## **PARTICIPANTS:**

### FDA:

Robert Justice, M.D., Director, DDOP  
Ann Farrell, M.D., Acting Deputy Director, DDOP  
Ramzi Dagher, M.D., Medical Team Leader, DDOP  
Maitreyee Hazarika, M.D., Medical Officer, DDOP  
Shwu-Luan Lee, PhD, Pharmacology-Toxicology Reviewer, DDOP  
John Leighton, PhD., Pharmacology Toxicology Team Leader  
Chia-wen Ko, PhD, Statistical Reviewer  
Qi Lu, PhD., Clinical Pharmacology Reviewer  
Roshni Ramchandani, PhD., Clinical Pharmacology, QT Reviewer  
Joanne Zhang, PhD, Statistical QT Reviewer  
Brian Booth, PhD., Team Leader Clinical Pharmacology  
Karen Hicks, M.D. Medical Officer QT  
J. Lloyd Johnson, Pharm D, Pharmacologist, GCPII, DSI (teleconference participant)  
Kathy Oh, DDMAC  
Robert J. Lechleider, M.D., NCI-FDA IOTF Fellow  
Janet Jamison, Project Manager, DDOP  
Dottie Pease, Chief Project Management Staff, DDOP

### Novartis Pharmaceutical:

Robert Miranda, Director Drug Regulatory Affairs (DRA)  
Nancy DelViscio, CMC-DRA  
Danielle Roman, Preclinical Safety  
Chiaki Tanaka, Pharmacology/DMPK  
Aaron Weitzman, Clinical Development  
Ming Zheng, Biostatistics

Bernd Eschgfäller, Project Management  
Joseph Quintavalla, DRA  
Prem Narang, Drug Regulatory Affairs

**MEETING OBJECTIVES:** Inform sponsor of the general progress and status of the review of their application to date.

**BACKGROUND:** NDA 22-068 was filed on September 29, 2006 for Tasigna® (nilotinib) in the treatment of chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to  prior therapy including Gleevec® (imatinib). The sponsor requested a 90 Day Post Submission Conference in the application in accordance with 21CFR 314.102(c). A 30 minute teleconference was scheduled between FDA staff and Novartis. During January 2007, three questions were communicated to Janet Jamison, PM by e-mail from Novartis related to general areas of interest in status of the review of the application.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

**Sponsor Question:**

1. What is the status of the trade name review? This was originally submitted to the FDA under the IND 69764, SN 201, March 23, 2006.

**FDA Response:**

A status update on the proposed trade name has not been received to date.

**Sponsor Question:**

\_\_\_\_\_

**Sponsor Question:**

3. Is there a projected review completion date? (To allow Novartis to plan for submission of all promotional pieces for review prior to approval).

**FDA Response:**

The application is under review and on track. The PDUFA goal date is July 29, 2007. An earlier completion date cannot be stated at this point in time.

**Discussion-FDA:**

The sponsor was informed that their responses to the queries and clarifications communicated to them previously have been reviewed. Follow-up questions on their responses will be forthcoming. As the review continues it is anticipated that future queries and clarifications would be forthcoming.

The review of cardiac safety data is in progress. A data clarification request will be forthcoming later today for (1) the datasets and program files for the additional concentration QTc analyses conducted for study 2119 and (2) a list of patients in the phase 2 components of study 2101, that received the FMI formulation and those that received the CSF formulation.

**Discussion-Sponsor:** The sponsor expressed an interest in any timely feedback on areas of the application review in particular the status of CMC review/completion date, GMP site audits needed, SPA review response, and the status of clinical study site audit requests for GCPs.

Maitreyee Hazarika, M.D. chaired the meeting. Janet Jamison facilitated the meeting.

**DECISIONS REACHED/ACTION ITEMS:**

- A request for QTc data clarification will be forthcoming today to the sponsor to be sent by Janet Jamison, PM.
- Janet Jamison, PM will follow up on the status of the trade name review and inform the sponsor.

The meeting was adjourned at 1:30 PM, EST.

Prepared by:

Janet Jamison, RN  
Project Manager, DDOP

Concurrence:

Maitreyee Hazarika, M.D.  
Medical Officer, DDOP

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/s/

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Maitreyee Hazarika  
2/5/2007 03:56:02 PM

**Jamison, Janet**

---

**From:** robert.miranda@novartis.com  
**Sent:** Friday, January 12, 2007 3:07 PM  
**To:** Jamison, Janet  
**Subject:** Re: N22-068 Tasigna Data Request  
**Attachments:** emfalert.txt

Thanks Janet. We are working on these requests.

\*\*\*\*\*

**Robert A. Miranda**  
**Director**  
**Drug Regulatory Affairs**  
**Oncology Business Unit**  
Building 104/ Room 2G37  
Novartis Pharmaceuticals  
One Health Plaza  
East Hanover, New Jersey 07936  
**Phone:** 862-778-2282  
**Fax:** 973-781-5217  
**E-mail:** [Robert.Miranda@Novartis.com](mailto:Robert.Miranda@Novartis.com)  
**Assistant:** Diana Arteaga +1 (862) 778-8784

\*\*\*\*\*

"Jamison, Janet" <[Janet.Jamison@fda.hhs.gov](mailto:Janet.Jamison@fda.hhs.gov)>

01/12/2007 02:17 PM

To: robert.miranda@novartis.com  
cc:  
Subject: N22-068 Tasigna Data Request

Hi Bob,

I am forwarding the 2 comments requested from Clinical Pharmacology during the T-Con meeting today.

- We have not received the datasets and program files for the additional concentration QTc analyses conducted for study 2119 (models relating delays in maximum concentration, maximum response and Emax model relating concentration). Please submit the datasets and the analyses files.
- Please provide a list of patients in the phase 2 components of study 2101, that have received the FMI formulation and a list of those that have received the CSF formulation.

I will attempt again to get a status update on the trade name review. I will include that in my final summary of today's meeting with other comments.

I will be in touch.

Janet

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
E-Mail: [janet.jamison@fda.hhs.gov](mailto:janet.jamison@fda.hhs.gov)

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/s/

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Janet Jamison  
1/31/2007 12:42:40 PM  
CSO

## Jamison, Janet

---

**From:** Jamison, Janet  
**Sent:** Wednesday, January 31, 2007 1:46 PM  
**To:** 'robert.miranda@novartis.com'  
**Cc:** 'joseph.quintavalla@novartis.com'  
**Subject:** N22068 Tasigna-FDA Request for Information

Hi Bob,

The reviewers have requested the following information related to the Tasigna application data:

1. Upon review of datasets A\_BMA and A\_FIS, it appears that the following 12 patients did not have adequate bone marrow or FISH for baseline diagnosis. Please submit documentation to justify their inclusion in the CML-CP dataset. Please justify their inclusion for cytogenetic responses.

0301\_04003  
0305\_04005  
0305\_04019  
0306\_04003  
0306\_04004  
0502\_04001  
0603\_04001  
0603\_04002  
0702\_04004  
0801\_04002  
0350\_04003  
0351\_04003

2. Upon review of datasets A\_BMA and A\_FIS, it appears that the following 13 patients did not have adequate bone marrow or FISH for baseline diagnosis. Please submit documentation to justify their inclusion in the CML-AP dataset.

0301\_03004  
0302\_03002  
0303\_03002  
0308\_03001  
0401\_03002  
0401\_03004  
0401\_03004  
0501\_03004  
0504\_03001  
0605\_03001  
0801\_03001  
0804\_03002  
0901\_03001

3. The CSR states that patient numbers were assigned sequentially. We note that follow-up information on patients enrolled appears sporadic. For example, in the CML-CP datasets, follow-up is provided for patients # 0250\_04001, 0250\_04002, 0250\_04003, and 0250\_04006. However, follow-up information is not available for patients # 0250\_04004 and 0250\_04005. If enrollment is sequential, then follow-up should be available. Please clarify the apparent discrepancy in both the CML-CP and CML-AP

datasets.

4. In the 132 CML-CP patients, 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. In the 64 CML-AP patients, 8 patients were recorded to have discontinued due to adverse events in the dataset with 6 explanations given in dataset A\_CMP.xpt. Please submit the adverse events for discontinuation in those not submitted. Also submit the reason for “administrative problems” for patient #0304-03006.
5. Please clarify how the hematologic response assessments (initial, confirmed and overall) were made. Clarify whether an “independent” investigator was used.
6. In dataset A\_EFFSBJ.xpt, both “BKR” and “CYTRES6C” = “Best cytogenetic response”. Please clarify the differences.

Regards,  
Janet Jamison

Project Manager  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2335  
Silver Spring, MD 20993  
301-796-2313  
E-Mail: janet.jamison@fda.hhs.gov

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/s/

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Janet Jamison  
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**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-068 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Tasigna  
Established Name: nilotinib  
Strengths: Capsules (200 mg)

Applicant: Novartis Pharmaceuticals Corporation  
Agent for Applicant (if applicable): N/A

Date of Application: September 29, 2006  
Date of Receipt: September 29, 2006  
Date clock started after UN: N/A  
Date of Filing Meeting: November 21, 2006  
Filing Date: November 28, 2006  
Action Goal Date (optional): July 27, 2007 User Fee Goal Date: July 29, 2007

Indication(s) requested: Treatment of chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to  prior therapy including Gleevec (imatinib).

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 1  
Other (orphan, OTC, etc.) Orphan (V)

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.

*Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES

**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, \_\_\_\_\_ Years NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES  NO

**Orphan product- PREA does not apply**

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**

*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO
- PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: IND 69,764

- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) December 2, 2005 NO

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) April 24, 2006 (f/u on 5/8/06 and 5/30/06) NO   
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO   
  
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO  N/A

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO

- |   |  |     |                                     |    |                          |
|---|--|-----|-------------------------------------|----|--------------------------|
|   | If EA submitted, consulted to EA officer, OPS?               | YES | <input type="checkbox"/>            | NO | <input type="checkbox"/> |
| • | Establishment Evaluation Request (EER) submitted to DMPQ?    | YES | <input checked="" type="checkbox"/> | NO | <input type="checkbox"/> |
| • | If a parenteral product, consulted to Microbiology Team? N/A | YES | <input type="checkbox"/>            | NO | <input type="checkbox"/> |

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: November 21, 2006

NDA #: 22-068

DRUG NAMES: Tasigna (nilotinib) Capsules

APPLICANT: Novartis Pharmaceuticals Corporation

**BACKGROUND:**

This is new molecular entity. The indication under review in this NDA received Fast Track designation on May 11, 2006. The first piece of this rolling NDA was submitted on August 9, 2006, and contained the CMC section. The final piece which completed the NDA was submitted on September 29, 2006.

**ATTENDEES:**

- Ramzi Dagher, MD, Acting Deputy Director
- Maitreyee Hazarika, MD, Clinical Reviewer
- Ann Farrell, MD, Clinical Team Leader
- Janet Jiang, PhD, Statistical Reviewer
- Raji Sridhara, PhD, Statistical Team Leader
- Luan Lee, PhD, Pharm/Tox Reviewer
- John Leighton, PhD, Pharm/Tox Team Leader
- Qi Liu, PhD, Clin Pharm Reviewer
- Roshni Ramchandani, PhD, Clin Pharm Reviewer
- Julie Bullock, PharmD, Clin Pharm Reviewer
- Janet Jamison, Project Manager
- Christy Cottrell, Project Manager

**ASSIGNED REVIEWERS (including those not present at filing meeting) :**

**Discipline/Organization**

**Reviewer**

Medical:	Maitreyee Hazarika, MD
Secondary Medical:	Ann Farrell, MD
Statistical:	Janet Jiang, PhD
Pharmacology:	Shwu-Luan Lee, PhD
Statistical Pharmacology:	
Chemistry:	William Timmer, PhD
Environmental Assessment (if needed):	
Biopharmaceutical:	Qi Liu, PhD (Roshni Ramchandani, PhD- QT)
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	David Gan, MD
OPS:	
Regulatory Project Management:	Christy Cottrell/Janet Jamison
Other Consults:	Joe Grillo (DDMAC)
	DMETS
	QT group (CDER DCRP QT)
	Statistics for stability (Roswitha Kelly)

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE   
 • Clinical site audit(s) needed? YES  NO   
 If no, explain:  
 • Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO   
 • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

• Biopharm. study site audits(s) needed? YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE

• GLP audit needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE

• Establishment(s) ready for inspection? YES  NO

• Sterile product? YES  NO

If yes, was microbiology consulted for validation of sterilization? YES  NO

**ELECTRONIC SUBMISSION:**

Any comments: None

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

**(Refer to 21 CFR 314.101(d) for filing requirements.)**

The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional): PLR formatting comments and a request for updated stability data on DP and DS.

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5.  Convey document filing issues/no filing issues to applicant by Day 74.

Christy Cottrell  
Regulatory Project Manager

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

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Christy Cottrell  
12/20/2006 03:30:38 PM  
CSO

**Tasigna® (nilotinib) capsule**  
**NDA 22-068**  
**December 18, 2006**

**Responses to FDA Clinical Review Comments of 12/15/06**

The following FDA review comments for NDA 22-068 were received via e-mail (Janet Jamison/Robert Miranda) on December 15, 2006. The Novartis response is provided after each FDA comment.

**FDA Comment 1.** Please explain the discrepancy seen in dataset A\_PTM.xpt and Table 3.2, SCE, in the number of patients with prior interferon (84 patients vs. 53 patients) and prior transplant (14 vs. 1) in the 132 patients with CML-CP. All different interferon treatments should be included. There also appears to be a discrepancy seen in dataset A\_PTM.xpt and table 3.7, SCE in the number of patients who received prior interferon and transplant in the 64 patients with CMP-AP.

**Novartis response:** FDA correctly points out these discrepancies between the SCE and the database. In Table 3.2 the number 53 refers to the number of patients who received prior interferon (preferred term: interferon). Novartis has conservatively estimated the full extent of prior interferon use and prior transplantation. When accounting for all types of prior interferon usage listed in PTT 14.3-1.11 for CML-CP (Preferred terms include: Interferon, Interferon Alfa, Interferon Alfa-2A, Interferon Alfa-2B, Interferons, Peginterferon Alfa-2A, Peginterferon Alfa-2B), 91 patients had received prior therapy with an interferon agent.

Similarly, when accounting for all types of prior interferon usage listed in PTT 14.3-1.11 for CML-AP (Preferred terms include: Interferon, Interferon Alfa, Interferon Alfa-2B, Peginterferon Alfa-2A), 37 patients had received prior therapy with an interferon.

The Table 3.2 showed that only 1 CP patient has prior stem cell transplant. Prior transplantation (both stem cell and non stem cell) in CML-CP and -AP occurred in 14 and 3 patients, respectively (Preferred term was Non Drug Organ Transplant, PTT 14.3-1.11).

**FDA Comment 2.** Please explain the discrepancy between Table PTT 14.1-1.1 and Table PTT 14.3-1.1.24 regarding AEs associated with discontinuation in the primary population in CSR, CAMN107A2101E2. The former shows 26 patients; the latter shows 29 patients.

**Novartis response:** Table PTT 14.3-1.1.24 indicates that in total, 29 patients experienced an adverse event associated with discontinuation. Of these 29 patients, 3 discontinued nilotinib therapy for another primary reason other than an adverse event (primary reason was provided by the investigator and recorded in the Study phase completion page of the CRF and can be found in PTL 16.2.1-1.1)

Therefore there were only 26 patients who discontinued nilotinib therapy due to adverse event as a primary reason (Table PTT 14.1-1.1). The primary reason for discontinuation for the three referenced patients was provided by the investigator and recorded in the Study phase completion page of the CRF and can be found in PTL 16.2.1-1.1 as follows:

Patient 0350\_04006 discontinued due to death.

Patient 0508\_04007 discontinued due to disease progression

Patient 0512\_04001 discontinued due to disease progression

**FDA Comment 3.** In datasets A\_DMG, please clarify that BLCHROM stands for baseline chromosome not Ph+. Also clarify what the responses 'Yes' and 'No' actually mean. Please confirm that the datasets show that it was not Ph+ in 108 patients out of the 132 efficacy patients in CML-CP and in 44 patients out of the 64 with CML-AP. Please indicate where this data was captured in the CRF.

**Novartis response:** The variable BLCHROM = Chromosomal abnormalities other than Philadelphia chromosome (see CRF panel BMA). "Yes" = patient had chromosomal abnormalities other than Philadelphia chromosome. "No" = patient did not have chromosomal abnormalities other than Philadelphia chromosome.

As indicated in PTT 14.1-3.5, four CML-CP patients had 0 Ph+ Chromosomes at baseline as determined by cytogenetic or FISH analysis. All of these four Ph negative CML-CP patients were noted at baseline to have the presence of the Bcr-Abl transcript in peripheral blood measured by PCR analysis thus establishing the diagnosis of CML. All CML-AP patients were noted to have the presence of the Ph+ chromosome.

**FDA Comment 4.** Please indicate where the laboratory data was captured in the CRF relevant to the definitions of chronic phase and accelerated phase as documented in dataset A\_DMG.

**Novartis Response:** All relevant laboratory and bone marrow data were collected in the CRF panels LRS (CBC data), BMA (bone marrow data) and FIS (FISH analysis). The determination of disease phase was made on the basis of these data regardless of investigator's assessment of disease phase.

**FDA Comment 5.** Upon review of dataset A\_HIS, it appears that the following 50 patients met criteria 1 but not 2 and were also not intolerant. Please submit any data to explain why they were identified as resistant CML-CP.

**Novartis Response:**

To qualify as imatinib resistant, both criteria 1 and 2 must have been met. As outlined in FDA question # 5, the 50 patients listed met imatinib resistance criteria # 1. Below is a by-patient listing providing the eligibility criteria as they relate to having met criteria # 2 (reason for resistance must have occurred at a dose  $\geq$  600 mg/day of imatinib) for demonstration of imatinib resistance (source documents: PTL 16.2.4-1.3, PTL 16.2.4-1.4):

0250\_04001 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0301\_04006 did not receive  $\geq$  600 mg/day of imatinib for at least 3 months but  
was assessed by the investigator as imatinib resistant  
0302\_04005 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0302\_04006 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0302\_04009 did not receive  $\geq$  600 mg/day of imatinib for at least 3 months but  
was assessed by the investigator as imatinib resistant  
0304\_04002 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0304\_04008 did not receive  $\geq$  600 mg/day of imatinib for at least 3 months but  
was assessed by the investigator as imatinib resistant  
0304\_04010 did not receive  $\geq$  600 mg/day of imatinib for at least 3 months but  
was assessed by the investigator as imatinib resistant  
0304\_04011 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0304\_04012 did not receive  $\geq$  600 mg/day of imatinib for at least 3 months but  
was assessed by the investigator as imatinib resistant  
0305\_04005 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0305\_04006 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0305\_04008 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0305\_04019 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0305\_04020 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0306\_04003 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0306\_04004 did not receive  $\geq$  600 mg/day of imatinib for at least 3 months but  
was assessed by the investigator as imatinib resistant. A query  
response from the site, as outlined in the attached file titled "scanned  
copy of query response", indicates that this patient was imatinib  
intolerant on the basis of recurrent thrombocytopenia.  
0350\_04001 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0350\_04009 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0350\_04011 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0351\_04003 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0351\_04006 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0352\_04003 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0401\_04003 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0402\_04002 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0501\_04003 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0501\_04006 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0502\_04001 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0502\_04009 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0502\_04010 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0502\_04012 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0502\_04016 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0503\_04001 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0508\_04001 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0508\_04003 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0508\_04004 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0508\_04005 received imatinib dose  $\geq$  600 mg/day for at least 3 months

0508\_04007 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0516\_04001 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0518\_04001 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0601\_04002 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0601\_04003 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0603\_04001 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0603\_04002 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0605\_04001 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0605\_04004 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0702\_04001 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0702\_04007 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0901\_04001 received imatinib dose  $\geq$  600 mg/day for at least 3 months  
0901\_04004 received imatinib dose  $\geq$  600 mg/day for at least 3 months

**FDA Comment 6.** In the CML-CP dataset A\_HIS, patient 0303\_04002 was called intolerant, but did not meet the definition of intolerance. Please submit any data in support.

**Novartis response:** As captured in the comments page of the CRF (PTL 16.2.9-1.6), patient 0303\_04002 was determined by the investigator to be imatinib intolerant on the basis of hemolytic anemia under treatment with imatinib.

**FDA Comment 7.** The five patients below in the CML-CP dataset received less than 600 mg and met criteria 1 (dataset A\_HIS) but not criteria 2 of the resistant definition. Please submit data to support their inclusion.

0301\_04006  
0302\_04009  
0304\_04008  
0304\_04010  
0306\_04004

**Novartis Response:** The determination of imatinib resistance in the absence of having been treated with imatinib 600 mg/day was made by the investigator as demonstrated in PTL 16.2.4-1.4.

**FDA Comment 8.** Dataset A\_DMG reveals that these 27 patients did not meet the definition of chronic phase in the 132 CML-CP efficacy patients. Please submit any data to support their inclusion.

**Novartis Response:** The following rule regarding the eligibility of CML-CP patients was established prior to database lock and can be found on page 10 in the Research Analysis Plan dated July 25th 2006, Module 3 Detailed statistical methodology Amendment 2 (see quote below and attached file for reference):

*"If a patient can not be assessed for CML-CP criteria at baseline due to missing LAB, BM or EMD values, then the patient's baseline cytogenetics will be used and if there is a Philadelphia positive chromosome present at baseline for any patient, that patient will be considered as satisfying the CML-CP criteria at baseline."*

All patients listed below as having missing baseline data did have baseline laboratory data and an assessment for their EMD status (presence of extramedullary disease) confirming the presence of chronic phase disease. Missing however, were the complete results from a valid baseline bone marrow assessment.

**Rationale for including patients missing a valid (and complete) baseline bone marrow assessment:** Philadelphia chromosome positivity is highly associated with the diagnosis of CML, to the extent of being a primary defining feature of the disease. Since cytogenetic response was the primary outcome being assessed, so long as Philadelphia chromosome was present and no other available data such as peripheral blood counts contradicted the diagnosis of chronic phase stage of disease, primary response assessment was possible. The availability of a valid bone marrow assessment would only therefore serve to either confirm the presence of chronic phase disease or potentially establish the presence of a more advanced stage of disease (i.e. if the blast count was unexpectedly higher in the bone marrow). Since there are occasions in standard clinical practice where an adequate bone marrow assessment is not possible due to a "dry tap" or hypocellular marrow findings, these patients were included in the study and were regarded as having chronic phase disease.

Thus, if all other available data in a given patient are indicative of CML-CP disease in the setting of a missing baseline laboratory value, a Philadelphia chromosome present at baseline was deemed sufficient for establishing CML-CP. The following is a by-patient listing demonstrating eligibility as outlined in the above criteria (source: PTL 16.2.6-1.1 and PTL 16.2.6-1.2):

**0250\_04002** meets all criteria for the definition of CML-CP except for percent blasts in bone marrow which was not assessable.

**0250\_04003** meets all criteria for the definition of CML-CP except for percent blasts in bone marrow which was not assessable due to a "dry tap".

**0301\_04003** meets all criteria for the definition of CML-CP except for percent blasts in bone marrow which was not assessable due to a "dry tap".

**0302\_04003** meets all criteria for the definition of CML-CP except for percent blasts in bone marrow which was not assessable.

**0304\_04002** meets all criteria for the definition of CML-CP except for percent blasts in bone marrow which was not assessable due to "inadequate material".

**0304\_04003** meets all criteria for the definition of CML-CP except for percent blasts in bone marrow which was not assessable due to "inadequate material".

**0304\_04005** was classified as a non-CML-CP patient due to missing baseline laboratory values without evidence of Ph<sup>+</sup> chromosome at baseline and was thus considered a protocol violator.

**0304\_04007** was classified as a non-CML-CP patient due to having a baseline basophil count of 29% and was thus considered a protocol violator.

**0304\_04009** meets all criteria for the definition of CML-CP except for percent blasts in bone marrow which was not assessable due to "inadequate material".

**0304\_04011** was classified as a non-CML-CP patient due to having a baseline platelet count of 97x10E9/L and was thus considered a protocol violator.

**0304\_04013** was classified as CML-CP despite having a baseline platelet count of 92x10E9/L. Thrombocytopenia at baseline was determined by the investigator to be related to imatinib intolerance (this was an imatinib intolerant patient) rather than advanced disease.

**0305\_04001** was classified as CML-CP despite having a baseline platelet count of 54x10E9/L. Thrombocytopenia at baseline was determined by the investigator to be related to imatinib intolerance (this was an imatinib intolerant patient) rather than advanced disease.

**0305\_04006** meets all criteria for the definition of CML-CP except for percent blasts in bone marrow which was not assessable.

**0305\_04007** was classified as a non-CML-CP patient due to baseline bone marrow obtained 47 days prior to start of study drug and was thus considered a protocol violator.

**0350\_04001** meets all criteria for the definition of CML-CP except for percent blasts and promyelocytes in bone marrow which was not assessable.

**0401\_04004** was classified as a non-CML-CP patient due to missing baseline laboratory values without evidence of Ph<sup>+</sup> chromosome at baseline and was thus considered a protocol violator.

**0502\_04004** was classified as a non-CML-CP patient due to baseline bone marrow obtained 33 days prior to start of study drug and was thus considered a protocol violator.

**0502\_04005** was classified as a non-CML-CP patient due to baseline bone marrow obtained 33 days prior to start of study drug and was thus considered a protocol violator.

**0502\_04009** appears to satisfy all criteria and was considered a CML-CP patient

**0508\_04003** was classified as CML-CP despite having a baseline platelet count of 84x10E9/L. Thrombocytopenia at baseline was determined by the investigator to be

related to imatinib intolerance (this was an imatinib intolerant patient) rather than advanced disease.

**0508\_04004** appears to satisfy all criteria and was considered a CML-CP patient

**0508\_04007** appears to satisfy all criteria and was considered a CML-CP patient

**0512\_04001** was classified as a non-CML-CP patient due to baseline bone marrow obtained 31 days prior to start of study drug and was thus considered a protocol violator.

**0519\_04003** was classified as CML-CP despite having a baseline platelet count of  $42 \times 10^9/L$ . Thrombocytopenia at baseline was determined by the investigator to be related to imatinib intolerance (this was an imatinib intolerant patient) rather than advanced disease.

**0603\_04002** was classified as a non-CML-CP patient due to baseline bone marrow obtained 31 days prior to start of study drug and was thus considered a protocol violator.

**0702\_04003** meets all criteria for the definition of CML-CP except for bone marrow sample which was "not evaluable".

**0702\_04007** meets all criteria for the definition of CML-CP except for percent blasts in bone marrow which was not assessable due to a "dry tap".

**FDA Comment 9.** In the dataset A\_HIS, the following 15 out of the 64 CML-AP efficacy patients are neither imatinib resistant nor intolerant. Please submit any data to explain why they have been included.

**Novartis Response:** The following is by-patient listing indicating criteria establishing imatinib resistance (source: PTL 16.2.4-1.4)

**0301\_03003** was classified as imatinib resistant on the basis of the investigator's assessment. Attached is a scanned copy of the query response from the investigator justifying inclusion of this patient.

**0301\_03007** was classified as imatinib resistant on the basis of the investigator's assessment. Attached is a scanned copy of the query response from the investigator justifying inclusion of this patient

**0301\_03008** was classified as having imatinib resistance on the basis of persistent disease for 2 or more weeks during imatinib therapy with  $\geq 600$  mg/day of imatinib

**0305\_03002** was classified as having imatinib resistance on the basis of persistent disease for 2 or more weeks during imatinib therapy with  $\geq 600$  mg/day of imatinib

**0305\_03006** was classified as having imatinib resistance on the basis of persistent disease for 2 or more weeks during imatinib therapy with  $\geq 600$  mg/day of imatinib

**0350\_03003** was classified as having imatinib resistance on the basis of persistent disease for 2 or more weeks and disease progression defined as a  $\geq 50\%$  increase in peripheral WBC count, blast count, basophil count or platelet during imatinib therapy with  $\geq 600$  mg/day of imatinib

**0350\_03004** was classified as having imatinib resistance on the basis of persistent disease for 2 or more weeks and disease progression defined as a  $\geq 50\%$  increase in peripheral WBC count, blast count, basophil count or platelet during imatinib therapy with  $\geq 600$  mg/day of imatinib

**0354\_03002** was classified as having imatinib resistance on the basis of persistent disease for 2 or more weeks during imatinib therapy with  $\geq 600$  mg/day of imatinib

**0401\_03003** was classified as imatinib resistant on the basis of the investigator's assessment.

**0504\_03006** was classified as having imatinib resistance on the basis of persistent disease for 2 or more weeks during imatinib therapy with  $\geq 600$  mg/day of imatinib

**0519\_03002** was classified as having imatinib resistance on the basis of disease progression defined as a  $\geq 50\%$  increase in peripheral WBC count, blast count, basophil count or platelet during imatinib therapy with  $\geq 600$  mg/day of imatinib

**0605\_03001** was classified as having imatinib resistance on the basis of persistent disease for 2 or more weeks during imatinib therapy with  $\geq 600$  mg/day of imatinib

**0804\_03001** was classified as having imatinib resistance on the basis of disease progression defined as a  $\geq 50\%$  increase in peripheral WBC count, blast count, basophil count or platelet during imatinib therapy with  $\geq 600$  mg/day of imatinib

**0860\_03001** was classified as having imatinib resistance on the basis of persistent disease for 2 or more weeks and disease progression defined as a  $\geq 50\%$  increase in peripheral WBC count, blast count, basophil count or platelet during imatinib therapy with  $\geq 600$  mg/day of imatinib

**FDA Comment 10.** In the dataset A\_DMG, the following 10 patients out of the 64 CML-AP efficacy patients do not fit the definition of accelerated phase. Please submit any data to explain why they have been included.

**Novartis response:** As outlined in section 3.3.2.1.2 of protocol CAMN107A2101, at least 1 of the following criteria present within 4 weeks prior to beginning treatment was required to establish accelerated phase disease:

- $\geq 15\%$  but  $< 30\%$  blast in blood or bone marrow
- $\geq 30\%$  blasts + promyelocytes in 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

The following is a by-patient listing of criteria establishing the definition of accelerated phase disease:

**0308\_03001** was classified as accelerated phase disease on the basis of a peripheral blast count of 17%

**0350\_03003** was classified as a non-CML-AP patient due to missing baseline bone marrow prior to start of study drug and was thus considered a protocol violator

**0350\_03004** was classified as accelerated phase disease on the basis of a peripheral blast count of 29%

**0501\_03008** was classified as accelerated phase disease on the basis of a peripheral blast count of 20%

**0503\_03002** was classified as accelerated phase disease on the basis of a peripheral blast count of 15%

**0503\_03005** was classified as a non-CML-AP patient due to baseline bone marrow being performed 29 days prior to start of study drug and was thus considered a protocol violator

**0504\_03001** was classified as accelerated phase disease on the basis of a peripheral basophil count of 26%

**0504\_03004** was classified as accelerated phase disease on the basis of thrombocytopenia of  $90 \times 10^9/L$  unrelated to prior therapy

**0504\_03006** was classified as accelerated phase disease on the basis of a peripheral basophil count of 22%

**0803\_03001** was classified as accelerated phase disease on the basis of a peripheral basophil count of 21%

**Attachments:**

1. Report Analysis Plan dated July 25th 2006, Module 3 Detailed statistical methodology Amendment 2
2. Scanned copy of the query responses from the investigator justifying inclusion of patients 0301\_03003 and 0301\_03007 as imatinib resistant.

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/s/

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Janet Jamison  
12/19/2006 08:35:39 AM  
CSO



NDA 22-068

**NDA ACKNOWLEDGMENT**

Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, NJ 07936-1080

Attention: Robert A. Miranda  
Director, Drug Regulatory Affairs

Dear Mr. Miranda:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tasigna® (nilotinib) Capsules, 200 mg  
Review Priority Classification: Standard (S)  
Date of Application: September 29, 2006  
Date of Receipt: September 29, 2006  
Our Reference Number: NDA 22-068

The application was filed on November 28, 2006, in accordance with 21 CFR 314.101(a). The user fee goal date is July 29, 2007.

We will review this application under the provisions of 21 CFR 314 Subpart H (accelerated approval). Before approval of this application, you must submit copies of all promotional materials, including promotional labeling as well as advertisements, to be used within 120 days after approval.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

NDA 22-068

Page 2

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Oncology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 796-1347.

Sincerely,

*{See appended electronic signature page}*

Christy Cottrell  
Consumer Safety Officer  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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/s/

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Christy Cottrell  
12/12/2006 02:58:16 PM

## TELECONFERENCE MEETING MINUTES

**MEETING DATE:** November 30, 2006 **TIME:** 10:30 A.M. (EST)

**LOCATION:** FDA White Oak Facility, Conference Room 2201

**NDA: 22-068** Meeting Request Submission Date: November 27, 2006  
Briefing Document Submission Date: November 27, 2006

**DRUG:** Tasigna® (nilotinib)

**INDICATION:** Chronic Myelogenous Leukemia, CP and AP

**SPONSOR:** Novartis Pharmaceutical Corporation

**TYPE OF MEETING:** A: Discuss sponsor request and rationale for consideration of priority review of NDA 22-068 and the agency's response.

### **PARTICIPANTS:**

#### FDA:

Robert Justice, M.D., Director, DDOP  
Ramzi Dagher, M.D., Acting Deputy Director, DDOP  
Maitreyee Hazarika, M.D., Medical Officer, DDOP  
Robert J. Lechleider, M.D., NCI-FDA IOTF Fellow  
Janet Jamison, Project Manager, DDOP  
Christy Cottrell, Consumer Safety Officer, DDOP

#### Novartis Pharmaceutical:

Aaron Weitzman, Clinical, Research and Development  
Bernd Eschgfäller, Project Management  
Robert Miranda, Drug Regulatory Affairs  
Prem Narang, Drug Regulatory Affairs  
Dr. Hagop Kantargian, University of Texas, MD Anderson Cancer Center, Houston, Texas

**MEETING OBJECTIVES:** Discuss proposed sponsor rationale to support a priority review request for NDA 22-068 and reach an agreement with FDA regarding review status determination.

**BACKGROUND:** NDA 22-068 was filed on September 29, 2006 for Tasigna® (nilotinib) in the treatment of chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to  prior therapy including Gleevec® (imatinib). The sponsor requested a priority review. In a telephone conversation on November 22, 2006, between Christy Cottrell (DDOP) and Robert Miranda (Novartis), the sponsor was notified that NDA 22-068 was given a standard review designation.

This meeting was requested by the sponsor to discuss their rationale for requesting a priority review for NDA 22-068. Background material and slides were submitted via email on November 27 and 29, 2006, respectively.

**DISCUSSION:**

The meeting began with a review of the Power Point slides (10) received from Novartis on November 29, 2006, titled: Tasigna® NDA 22-068 Priority Review Request, by Novartis participants. This was followed by a discussion which included the previous FDA notification of standard review designation for this NDA. Maitreyee Hazarika, M.D. chaired the meeting. Christy Cottrell facilitated the meeting.

(Copy of Novartis slides inserted)

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On Original**

2   Page(s) Withheld

  ✓   Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

**SPONSOR QUESTION:** Does FDA agree that the criteria described supports an unmet medical need and that a priority review is appropriate?

**FDA RESPONSE:**

We do not agree with your request for priority designation. The determination of a standard designation is based on the following:

1. Nilotinib does not have an increased effectiveness compared to dasatinib. In both populations, CML-CP and CML-AP, the response rates appear lower with nilotinib compared to dasatinib.
2. The adverse events of nilotinib may be different from dasatinib. However, there has been a QT prolongation signal and several sudden deaths with nilotinib. This needs further review. The nilotinib safety dataset is less robust with a shorter follow-up. It is difficult to make comparative safety claims without a randomized study.
3. The indication for nilotinib is in a similar population for which dasatinib has been approved.

In conclusion, the nilotinib application does not suggest that the drug product, if approved, would be a significant improvement over marketed products.

**DECISION:** The FDA determined a standard review designation for nilotinib (NDA 22-068).

The meeting was adjourned at 11:00 A.M., EST.

Prepared by:

Janet Jamison, RN  
Project Manager, DDOP

Concurrence:

Maitreyee Hazarika, M.D.  
Medical Officer, DDOP

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/s/

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Maitreyee Hazarika  
12/1/2006 02:34:39 PM

**REQUEST FOR CONSULTATION**

TO (Division/Office):  
Interdisciplinary Review Team for QT Studies  
Attention: Devi Kazeli and/or Denise Hinton

FROM:  
HFD-150/Division of Drug Oncology Products  
Christy Cottrell, Consumer Safety Officer

DATE  
November 1, 2006

IND NO.

NDA NO.  
NDA 22-068

TYPE OF DOCUMENT  
N-doc

DATE OF DOCUMENT  
September 29, 2006

NAME OF DRUG  
Tasigna (nilotinib)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
January 15, 2007

NAME OF FIRM: Novartis

**REASON FOR REQUEST**

**I. GENERAL**

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING            | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING    | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION               | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input checked="" type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA                  | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT         | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |   |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

- DISSOLUTION  
 BIOAVAILABILITY STUDIES  
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE  
 PROTOCOL-BIOPHARMACEUTICS  
 IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL  
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES  
 CASE REPORTS OF SPECIFIC REACTIONS (List below)  
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY  
 SUMMARY OF ADVERSE EXPERIENCE  
 POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

CLINICAL

PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**

This submission is a new NME NDA. The Division has two specific requests:  
1) Please review the thorough QT study (2119) conducted for nilotinib.  
2) Please also evaluate the concentration-QT relationship across the Phase 1/2 and thorough QT studies.  
The datasets, study reports and protocols are all available in the EDR. ECGs are available in the warehouse.

**Requested completion date: January 15, 2007.**

DDOP MO: Maitreyee Hazarika, MD

DDOP PM: Christy Cottrell (x61347)

METHOD OF DELIVERY (Check one)  
X MAIL

HAND

SIGNATURE OF RECEIVER

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Christy Cottrell

11/1/2006 02:56:12 PM

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available in the EDR. ECGs are in the  
warehouse.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): Division of Biometrics V Attention: Raji Sridhara, PhD		FROM: HFD-150/Division of Drug Oncology Products Christy Cottrell, Consumer Safety Officer		
DATE November 1, 2006	IND NO.	NDA NO. NDA 22-068	TYPE OF DOCUMENT N (000)	DATE OF DOCUMENT September 29, 2006
NAME OF DRUG Tasigna (nilotinib)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE April 1, 2007
NAME OF FIRM: Novartis				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Stability		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS.</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> This submission is a new NME NDA. As requested by the CMC team, please review for stability. The application is available in the EDR.  PDUFA DUE DATE: July 29, 2007 <b>Requested consult completion date: April 1, 2007</b>  DDOP MO: Maitreyee Hazarika, MD DDOP PM: Christy Cottrell (x61347)				
		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <span style="float: right;"><input checked="" type="checkbox"/> HAND</span>		
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/s/

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Christy Cottrell

11/1/2006 03:36:39 PM

DR: Please process this outgoing consult. The application is  
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**From:** Cottrell, Christy  
**Sent:** Wednesday, October 25, 2006 3:27 PM  
**To:** 'robert.miranda@novartis.com'; 'joseph.quintavalla@novartis.com'  
**Cc:** Cross Jr, Frank H  
**Subject:** NDA 22-068 for Tassigna (nilotinib)  
Bob,

Please refer to your pending NDA 22-068 for Tassigna (nilotinib). See below for two requests for additional information from the clinical pharmacology team.

1. Please clarify the bioanalytical method used for analysis of plasma samples in study 2119 and if it differs significantly from the method used in the earlier studies.
2. Please submit the data as SAS transport files for studies CAMN107A2104, CAMN107A2108, CAMN107A2110 and CAMN107A2106.

Feel free to call me if you have any questions.

Thanks,  
Christy

\*\*\*\*\*

*Christy Cottrell*  
*Consumer Safety Officer/Project Manager*  
*Division of Drug Oncology Products, FDA*  
*p: (301) 796-1347*  
*f: (301) 796-9845*  
*NEW EMAIL ADDRESS: christy.cottrell@fda.hhs.gov*

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/s/

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Christy Cottrell  
10/25/2006 03:41:24 PM  
CSO

**From:** Cottrell, Christy  
**Sent:** Tuesday, October 10, 2006 10:40 AM  
**To:** 'robert.miranda@novartis.com'  
**Subject:** NDA 22-068 for Tassigna  
Bob,

Please refer to your NDA 22-068 for Tassigna (nilotinib). See below for an inquiry from the clinical reviewer.

- Has Novartis submitted the ECG waveforms to the ECG warehouse? If not, when do you plan to do so?

Let me know if you have any questions.

Thanks,  
Christy

\*\*\*\*\*  
*Christy Cottrell*  
*Consumer Safety Officer/Project Manager*  
*Division of Drug Oncology Products, FDA*  
*p: (301) 796-1347*  
*f: (301) 796-9845*  
*NEW EMAIL ADDRESS: [christy.cottrell@fda.hhs.gov](mailto:christy.cottrell@fda.hhs.gov)*

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/s/

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Christy Cottrell  
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CSO