CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-335/S-004

Administrative Documents

Patent Submission

Time Sensitive Patent Information

Pursuant to 21 C.F.R. 314.53

for

NDA # 21-335

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Gleevec™
- Active Ingredient(s): imatinib mesylate
- Strength(s): 50 mg, 100 mg
- Dosage Form: Capsule
- Approval Date: Pending

A. This section should be completed for each individual patent

U.S. Patent Number: 5,521,184

Expiration Date: May 28, 2013

Type of Patent—Indicate all that apply:

1. Drug substance (Active Ingredient)	✓Y	N
2. Drug Product (Composition/Formulation	✓Y	N
3. Method of Use	Y	✓N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

Name of Patent Owner: Novartis Corporation

U.S. Agent (If patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 5,521,184 covers the composition, formulation and/or method of use of imatinib mesylate (STI571). This product is:

- Currently approved under section 505 of the Federal Food, Drug,

and Cosmetic Act)

or

- ✓ the subject of this application for which approval is being sought.)

Signed: George R Dohmann
George Dohmann

Title: Patent Attorney

Date: 5/21/02

Telephone Number: (908) 522-6922

EXCLUSIVITY SUMMARY for NDA # 21-335 SUPPL # 004
Trade Name Gleevec Generic Name imatinib mesylate
Applicant Name Novartis Pharmaceuticals HFD- 150
Approval Date December 20, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/___/ NO /___/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   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 /_X_/ 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 /_X__/

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 /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /__X_/ NO /___/

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

NDA # 21-335 Gleevec

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 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S 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 /__X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /_X_/ 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 9:**

_____

_____

(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 /_X__/

(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 /_X__/

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:

Investigation #1, Study # study 106

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /_X__/
Investigation #2	YES /___/	NO /___/
Investigation #3	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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /__X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study #_106_____

Investigation #_, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /_X__/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
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 /__X_/

If yes, explain: _____

_____

_____

Ann Staten,RD _____
Signature of Preparer Date
Title: Project Manager

Richard Pazdur,MD _____
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- 150 /Division File
HFD- 150 /AStaten
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Richard Pazdur
12/20/02 03:23:26 PM

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Gleevec™ (imatinib mesylate) Capsules
NDA 21-335 / S-002

(Newly Diagnosed CML Indication)

NOVARTIS CERTIFICATION IN COMPLIANCE WITH THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Novartis Pharmaceuticals Corporation 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.

5/31/02
Date

Robert A. Miranda
Director
Drug Regulatory Affairs

EXCLUSIVITY SUMMARY for NDA # 21-335 SUPPL # 004
Trade Name Gleevec Generic Name imatinib mesylate
Applicant Name Novartis Pharmaceuticals HFD- 150
Approval Date December, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/___/ NO /_X_/

b) Is it an effectiveness supplement? YES /_X_/ NO /___/

If yes, what type(SE1, SE2, etc.)? SE1

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 /_X_/ 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 /_X__/

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 /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /__X_/ NO /___/

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

NDA # 21-335 Gleevec

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /__X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /_X_/ 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 9:**

_____

_____

(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 /_X__/

(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 /_X__/

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:

Investigation #1, Study # study 106

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /_X__/
Investigation #2	YES /___/	NO /___/
Investigation #3	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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /__X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study #_106_____

Investigation #_, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /_X__/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

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 /__X_/

If yes, explain: _____

_____

_____

Ann Staten,RD _____
Signature of Preparer Date
Title: Project Manager

Richard Pazdur,MD _____
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- 150 /Division File
HFD- 150 /AStaten
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

MEMORANDUM

Date: December 16, 2002
From: John K. Leighton, Ph.D., DABT
Supervisory Pharmacologist, HFD-150
To: File for NDA #21-335, supplement 4
Re: Approvability for Pharmacology and Toxicology
Gleevec (imatinib mesylate)

Gleevec is an inhibitor of protein tyrosine kinase associated with Bcr-Abl, PDGF receptor, and cKit. Of particular importance for the proposed indication, treatment of patients with newly diagnosed Philadelphia positive chronic myeloid leukemia (CML), is the ability of imatinib to inhibit the Bcr-Abl associated TK, as this TK is thought to play a role in the aberrant proliferation of myeloid cells.

In this supplemental NDA, the Sponsor has provided additional information on the nature of parent compound and/or metabolites secreted into milk of lactating rats administered ^{14}C-imatinib mesylate In addition, the Sponsor conducted a pre- and postnatal developmental study in rats These studies were reviewed by Dr. Benson and the information incorporated into the revised label.

Recommendations: The pharmacology and toxicology data supports approval of this supplemental NDA. There are no outstanding issues.

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

/s/

John Leighton
12/16/02 01:59:11 PM
PHARMACOLOGIST

PROJECT MANAGER REVIEW OF LABELING

NDA 21-335/S-004

Drug: Gleevec (imatinib mesylate), 50 and 100 mg

Applicant: Novartis Pharmaceutical Corporation

Submission Date: June 28, 2002
Receipt Date: June 28, 2002

BACKGROUND:

Gleevec is approved for the treatment of patients with Philadelphia positive (Ph+) chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is also approved for the treatment of patients with kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

The current supplement S-004 provides for a new indication for the treatment of patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (CML). This supplement proposes changes to the following sections of the package insert: CLINICAL PHARMACOLOGY, CLINICAL STUDIES, PRECAUTIONS, and ADVERSE REACTIONS.

DOCUMENTS REVIEWED:

I compared the approved FPL dated March 6, 2002 to the proposed labeling in S-004 dated June 28, 2002.

REVIEW:

I found that all of the proposed changes to the package insert were identified by the underline and strikethrough feature.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

In this supplement, the sponsor has correctly identified all of the proposed changes to the package insert using the underline and strikethrough feature. This supplement may be approved with the concurrence of the medical, pre-clinical pharmacology/toxicology and clinical pharmacology reviewers.

___ *{See appended electronic signature page}*_
Ann Staten, Regulatory Health Project Manager

___*{See appended electronic signature page}*_
Dotti Pease, Chief, Project Manager Staff

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

/s/

Ann Staten
9/25/02 04:28:55 PM
CSO

Dotti Pease
9/26/02 07:07:49 AM
CSO

From: Staten, Ann M
Sent: Tuesday, December 17, 2002 11:50 AM
To: Robert Miranda (E-mail)
Subject: phase 4 commitments attached

Importance: High

Dear Bob,

Below are the two phase 4 commitments discussed at our telecon last Thursday. We will need your written agreement before an action can be taken.

Thanks,
Ann

Phase 4 commitment required for accelerated approval:

> To provide interval follow-up safety and efficacy information on study 106 annually for six additional years.

Phase 4 commitment: Gleevec-Rifampin interaction

> It is known that rifampin is a potent CYP3A4 inducer, and decreased Gleevec AUC by an average of 67 % in healthy normal volunteers.
>
> We request that a prospective study be performed in patients receiving both Gleevec and a potent CYP3A4 inducer such as phenytoin, phenobarbital, or carbamazepine and that the final study report be submitted for our review. The purpose of this study will be to determine the dose of Gleevec that is necessary to produce similar AUCs in these patients on enzyme inducers to those achieved in adult patients receiving the usual recommended dose (400 mg/day)
>
> Please submit a protocol for Agency review.

Staten, Ann M

From: robert.miranda@pharma novartis com
Sent: Friday, December 20, 2002 1 20 PM
To: Staten, Ann M
Subject: RE: PI

Dear Ann,

The PI is therefore acceptable to us as is. Thank you again for all your help.

Bob

"Staten, Ann M" <STATENA@cder.fda.gov> on 12/20/2002 01:16:43 PM

To: "'robert.miranda@pharma novartis.com'" <robert.miranda@pharma.novartis.com>
cc:
Subject: RE: PI

This part of the message was ENCRYPTED

This part of the message was SIGNED by Email=statena@cder.fda.gov, ou="This certificate represents a secure server, not an individual.", o=FDA/CDER, cn=FDA/CDER Secure Server (proxy), who is certified by Email=secure-server@CDER.FDA.GOV, ou="This certificate represents a secure server, not an individual.", o=FDA/CDER, cn=FDA/CDER Secure Server

Dear Bob,

We reviewed your request but we do not agree with the proposed change.

Ann

-----Original Message-----
From: robert.miranda@pharma.novartis.com [mailto:robert.miranda@pharma.novartis.com]
Sent: Friday, December 20, 2002 9:56 AM
To: statena@cder.fda.gov
Subject: PI
Importance: High

Hi Ann,

I met with the team and the PI is acceptable except we would like one word change in the QOL paragraph.

In line 186 can we change ____ to ____ which would read:

We feel this is appropriate since most of the QOL questions were general symptoms We acknowledge that a large part of the questions were interferon related, which is why we think this minor revision is appropriate.

Please call me if there is anything else you need from me. We are very happy with the level and results of the review, the labeling and your outstanding assistance in coordinating all these efforts.

Thanks,
Bob.....

Staten, Ann M

From: Staten, Ann M
Sent: Thursday, November 14, 2002 11:06 AM
To: Robert Miranda (E-mail)
Subject: Gleevec s-004 clinical questions

Importance: High

Dear Bob,

We have more questions for you in Word The SAS transport file identifies which patients we found to have confirmed cytogenetic responses and major cytogenetic responses


Nov 14 CyR's doc


Calculation of MCyR and C CyR

Per the protocol, Cytogenetic analysis were to be performed every three months for the first 12 months of therapy and every six months thereafter, and on the last day of treatment. Cytogenetic response were protocol defined in terms of the percentage of Ph chromosome-positive metaphases in bone marrow· complete response (0% Ph-positive cells); partial (> 0%-35%), minor (> 35%-65%), minimal (> 65%-95%); none (> 95%-100%). Complete and partial cytogenetic responses are referred to as major cytogenetic response, i e. < 35% of Ph chromosome-positive metaphases in bone marrow. The primary analysis will be intention-to-treat (end of phase 1 meeting 5/3/00).

The FDA minutes of the pre NDA meeting on 4/17/02 reflect that only confirmed cytogenetic responses should be counted. If an individual has a CCyR on one occasion and a PCyR on a different evaluation it will be scored as a PCyR, regardless of the order of the evaluations. If the order is reversed and no subsequent study is done it is still a PCyR Confirmed MCyR rate should therefore be derived from those patients who had no worse than a PCyR on any of their aspirates, and confirmed C CyR should be from patients who had no worse than a CCyR on any visit.

The sponsor either performed traditional or FISH analysis, either is acceptable The denominator I used was the number of patients with >1 aspirates adequate for cytogenetic analysis, rather than the total number of patients. I recalculated the confirmed ITT cytogenetic response rates on this basis and the results are summarized below:

Table 1: FDA confirmed Cytogenetic Response Rates

	Gleevec	IFN+Ara-C
N ≥1 adequate aspirates	533	490
Number (%) confirmed MCyR	326 (61%)	41 (8 3%)
95% C.I	57, 65	5.8, 10.7
Number (%) confirmed CCyR	146 (27.4%)	18 (3 7%)
95% C.I.	31.2, 23.6	5.4, 2 0

Please explain how the following cytogenetic response rates were derived

Table 2: Sponsor's Confirmed MCyR rate

Confirmed Cy Response Rate		
Number of MCyR	419 (75.8%)	67 (12.1%)
Number of CCyR	297 (53.7%)	15 (2.7%)

SID1A	adequate for C	n(STDDAx	(STDD	RNDTRT_N	Min(CyR)	Max(CyR)	MCyR	C CyR
0001_00001	3	0	257	2			0	0
0001_00002	6	0	504	1	1	2	1	0
0001_00003	4	-2	258	1	1	2	1	0
0001_00004	6	0	504	1	1	1	1	1
0001_00005	6	0	500	2			0	0
0001_00006	5	1	343	1	1	2	1	0
0001_00007	5	-3	347	2			0	0
0001_00008	3	-4	345	2	1	2	1	0
0001_00009	4	1	260	1	1	2	1	0
0002_00001	2	1	172	1	1	1	1	1
0002_00002	4	0	499	2			0	0
0002_00003	6	-10	508	1	1	1	1	1
0002_00004	4	1	337	2			0	0
0002_00006	3	-4	254	2	1	1	1	1
0002_00007	4	-2	253	1	1	2	1	0
0002_00008	4	0	255	1	1	1	1	1
0002_00009	5	-1	335	2			0	0
0002_00010	4	1	334	2			0	0
0003_00001	6	0	524	2			0	0
0003_00002	4	1	345	1			0	0
0003_00003	4	-2	257	1			0	0
0003_00004	5	-1	349	1			0	0
0004_00002	4	-1	342	2			0	0
0004_00003	6	1	514	1	1	2	1	0
0004_00004	3	85	341	1	1	1	1	1
0004_00005	3	-3	340	2			0	0
0005_00002	3	0	169	2			0	0
0005_00003	2	88	172	2			0	0
0006_00002	6	0	458	2			0	0
0006_00003	4	0	251	2			0	0
0006_00004	4	-4	358	2			0	0
0006_00005	5	-1	376	2			0	0
0006_00006	3	89	271	1	1	2	1	0
0006_00007	4	1	323	1	1	2	1	0
0007_00001	6	0	507	1	1	2	1	0
0007_00002	6	4	502	1	1	1	1	1
0007_00003	5	1	338	2			0	0
0008_00001	4	1	333	2			0	0
0008_00002	5	1	337	1	1	1	1	1
0008_00003	5	2	338	1	1	1	1	1
0008_00004	4	-25	255	2			0	0
0008_00005	3	1	246	1			0	0
0009_00001	4	-2	355	1	1	1	1	1
0009_00002	5	-4	331	2			0	0
0009_00003	5	1	339	1	1	2	1	0
0009_00004	5	-9	330	2			0	0
0010_00001	5	90	510	1	1	2	1	0
0010_00002	5	1	333	1	1	2	1	0
0010_00003	4	-6	249	2			0	0
0011_00001	5	1	344	1	1	2	1	0
0011_00002	3	202	384	2			0	0

0011_00003	5	-17	379	1			0	0
0011_00004	4	2	369	2			0	0
0011_00005	4	1	279	1	1	2	1	0
0011_00006	4	1	351	2			0	0
0011_00007	4	1	269	1	1	1	1	1
0012_00001	4	1	512	2			0	0
0016_00001	3	1	177	1	1	2	1	0
0017_00001	6	1	508	1	1	1	1	1
0017_00002	5	-2	344	1			0	0
0017_00003	3	1	344	1			0	0
0018_00001	5	1	503	2			0	0
0018_00002	6	1	501	2			0	0
0018_00003	6	-14	505	2			0	0
0018_00004	6	1	516	1	1	1	1	1
0018_00005	6	1	511	1			0	0
0018_00006	7	0	525	2			0	0
0018_00007	4	1	343	2			0	0
0018_00008	5	1	350	2			0	0
0018_00009	5	0	330	1			0	0
0018_00010	5	1	354	2			0	0
0019_00001	4	2	350	2			0	0
0019_00002	6	1	511	2			0	0
0019_00003	5	0	343	1	1	1	1	1
0019_00004	4	1	346	1	1	1	1	1
0019_00005	5	1	337	1	1	1	1	1
0019_00006	5	1	342	1	1	2	1	0
0019_00007	4	0	350	2	1	1	1	1
0019_00008	5	1	349	2			0	0
0020_00001	5	1	497	1	1	2	1	0
0020_00002	3	1	343	2			0	0
0020_00003	4	1	488	2			0	0
0026_00001	3	-2	505	2			0	0
0026_00002	6	0	504	2			0	0
0026_00003	5	-2	361	1			0	0
0026_00004	5	-6	350	1			0	0
0026_00005	5	-3	346	1	1	2	1	0
0026_00006	5	-5	329	2			0	0
0027_00001	4	-5	509	1	1	1	1	1
0027_00002	6	-2	459	1	1	1	1	1
0027_00003	5	1	340	1	1	2	1	0
0027_00004	4	1	348	1	1	1	1	1
0027_00005	4	0	350	1	1	1	1	1
0027_00006	5	-2	334	2			0	0
0028_00001	4	1	255	1			0	0
0028_00002	6	1	407	1			0	0
0028_00003	5	-155	344	1	1	1	1	1
0028_00004	4	1	357	2			0	0
0028_00005	5	1	354	1	1	1	1	1
0028_00006	5	0	352	1	1	1	1	1
0028_00007	5	13	364	2			0	0
0028_00008	4	7	259	2			0	0
0028_00009	3	-8	246	1			0	0

0028_00010	5	1	343	1	1	1	1	1
0028_00011	2	81	340	1			0	0
0029_00001	4	-6	333	1			0	0
0029_00002	2	-12	94	2			0	0
0029_00003	6	-11	507	1			0	0
0029_00004	7	-25	500	1	1	1	1	1
0029_00005	5	-19	338	1	1	1	1	1
0030_00001	4	0	339	2			0	0
0030_00003	5	-5	338	2			0	0
0030_00004	6	-3	344	2			0	0
0030_00005	4	-6	333	1	1	1	1	1
0031_00001	3	-7	169	2			0	0
0031_00002	2	-12	176	2			0	0
0031_00004	2	1	83	1			0	0
0031_00005	3	1	142	2			0	0
0032_00002	5	1	337	2			0	0
0032_00003	2	87	283	2			0	0
0033_00001	3	113	363	2			0	0
0033_00002	3	-15	196	2			0	0
0033_00003	3	87	331	1	1	2	1	0
0033_00004	2	104	180	2			0	0
0033_00005	3	-12	358	2			0	0
0033_00006	3	-24	212	2			0	0
0033_00007	4	1	284	2			0	0
0034_00001	5	0	354	1			0	0
0034_00002	4	4	368	1	1	1	1	1
0035_00001	3	-13	241	2			0	0
0035_00002	3	-12	344	2			0	0
0035_00003	5	0	377	2			0	0
0035_00004	5	1	337	1			0	0
0035_00005	5	1	330	1	1	2	1	0
0036_00001	4	-2	502	2			0	0
0036_00002	5	-4	346	2			0	0
0036_00003	5	-15	349	1	1	2	1	0
0036_00004	4	-2	260	1			0	0
0036_00005	6	-12	437	2			0	0
0036_00006	5	-3	350	1	1	1	1	1
0041_00001	4	1	262	1	1	2	1	0
0041_00002	6	1	506	1	1	2	1	0
0041_00004	4	-7	327	2			0	0
0042_00001	5	-4	345	1	1	2	1	0
0042_00002	5	3	346	1	1	1	1	1
0042_00003	5	7	344	1	1	1	1	1
0043_00001	7	0	505	1	1	2	1	0
0043_00002	6	1	505	2			0	0
0043_00003	6	1	505	2			0	0
0043_00004	6	-6	506	1	1	2	1	0
0043_00006	5	0	343	2			0	0
0043_00007	5	1	337	1	1	2	1	0
0043_00008	5	0	336	2			0	0
0043_00009	5	1	335	2			0	0
0046_00001	6	-2	518	1	1	2	1	0

0046_00002	5	1	380	1			0	0
0046_00003	5	1	351	2			0	0
0046_00004	4	1	386	2			0	0
0046_00005	5	-3	361	1	1	2	1	0
0046_00006	4	1	337	2			0	0
0046_00009	4	1	260	1			0	0
0047_00001	5	5	341	2			0	0
0047_00002	5	-11	338	2			0	0
0047_00003	5	-9	338	1			0	0
0047_00004	5	-11	339	1	1	2	1	0
0047_00005	5	1	338	1	1	2	1	0
0047_00006	5	1	355	2			0	0
0047_00007	5	1	337	1	1	1	1	1
0047_00008	4	-9	339	1	1	2	1	0
0047_00009	5	-8	338	2			0	0
0047_00010	5	-10	338	2			0	0
0047_00011	5	1	339	2	1	2	1	0
0048_00001	2	-6	127	2			0	0
0048_00002	2	-6	275	2	1	1	1	1
0048_00003	4	-6	345	2	1	2	1	0
0048_00004	5	5	295	1			0	0
0048_00005	5	1	343	2			0	0
0048_00006	5	1	342	2			0	0
0048_00007	5	3	338	1	1	2	1	0
0048_00009	5	2	344	1	1	1	1	1
0048_00010	2	1	281	1	1	1	1	1
0048_00011	4	1	331	2			0	0
0048_00012	3	-3	171	2			0	0
0049_00001	6	-6	512	1	1	2	1	0
0049_00002	4	-5	253	1			0	0
0049_00003	4	1	257	1			0	0
0050_00001	5	-5	518	1	1	1	1	1
0050_00002	5	-11	346	2			0	0
0050_00003	4	-18	246	2			0	0
0050_00004	5	-13	336	1	1	1	1	1
0050_00005	5	-1	336	1	1	1	1	1
0050_00006	5	0	341	2			0	0
0050_00007	5	-6	379	1	1	1	1	1
0050_00008	5	-19	343	1			0	0
0050_00009	5	-6	339	1	1	1	1	1
0050_00010	3	1	358	2			0	0
0051_00001	6	-1	510	2			0	0
0051_00002	6	0	511	1			0	0
0051_00003	5	0	380	1			0	0
0051_00004	5	0	378	1			0	0
0051_00005	5	-1	341	2			0	0
0051_00006	5	0	350	2			0	0
0051_00007	4	1	260	2			0	0
0052_00001	4	3	340	1	1	1	1	1
0052_00002	4	-3	246	2			0	0
0052_00003	4	0	273	2	1	2	1	0
0053_00001	5	1	339	1	1	1	1	1

0053_00002	3	1	337	2			0	0
0053_00003	4	1	346	1			0	0
0053_00004	5	-9	341	2			0	0
0054_00001	5	-6	376	2			0	0
0054_00002	5	-6	477	2			0	0
0054_00003	5	-6	338	2			0	0
0054_00004	6	-6	505	2			0	0
0054_00005	5	-6	337	2			0	0
0054_00006	5	-6	500	2			0	0
0054_00007	5	-6	337	1			0	0
0054_00008	4	-6	281	2			0	0
0054_00009	4	-5	337	2			0	0
0054_00010	4	-6	253	1			0	0
0054_00011	3	169	337	1	1	1	1	1
0054_00012	5	-6	339	1	1	2	1	0
0054_00013	4	-6	330	1			0	0
0054_00014	5	-6	340	1	1	2	1	0
0054_00015	5	-6	337	1	1	1	1	1
0054_00016	5	-6	336	1	1	2	1	0
0055_00001	6	-12	499	2			0	0
0055_00002	5	-5	507	1	1	2	1	0
0055_00003	3	-11	506	1			0	0
0055_00004	4	-2	350	1	1	2	1	0
0055_00005	4	-5	339	1			0	0
0055_00006	4	-4	255	1			0	0
0055_00007	5	-3	338	1			0	0
0055_00008	2	-5	264	2			0	0
0055_00009	3	-6	337	2			0	0
0055_00010	4	-6	260	2	1	2	1	0
0055_00011	5	-5	340	2			0	0
0055_00012	3	1	169	1	1	2	1	0
0060_00001	2	-8	97	1			0	0
0060_00002	3	-3	172	1	1	2	1	0
0060_00003	4	1	372	2			0	0
0060_00004	4	18	365	1			0	0
0060_00005	5	1	341	1			0	0
0060_00006	5	0	357	1	1	2	1	0
0061_00001	3	6	510	2			0	0
0061_00003	5	-3	339	1	1	2	1	0
0062_00001	7	-14	509	1			0	0
0062_00002	6	-20	510	1	1	2	1	0
0063_00001	5	-12	536	2			0	0
0063_00002	5	1	369	1	1	2	1	0
0063_00003	5	7	357	1			0	0
0064_00001	5	-13	511	1			0	0
0065_00001	5	-2	512	1	1	1	1	1
0065_00002	6	-3	508	1	1	1	1	1
0065_00003	6	-12	507	2			0	0
0065_00004	3	1	169	2			0	0
0065_00005	6	-12	507	2			0	0
0065_00006	6	-2	511	1			0	0
0065_00007	7	1	514	2			0	0

0065_00008	6	-3	513	2			0	0
0065_00009	6	-3	507	1	1	2	1	0
0065_00010	5	1	509	1	1	1	1	1
0065_00011	4	-5	499	2			0	0
0065_00012	2	-13	169	2			0	0
0065_00013	4	85	498	2			0	0
0065_00014	5	-7	338	2			0	0
0065_00015	5	1	339	1	1	1	1	1
0065_00016	3	-1	378	1	1	2	1	0
0065_00018	5	-10	358	1	1	1	1	1
0065_00019	2	-13	173	2			0	0
0065_00020	4	1	344	2			0	0
0065_00021	3	1	171	1			0	0
0065_00022	4	7	378	1	1	2	1	0
0065_00023	4	-1	358	2			0	0
0065_00024	3	1	261	1	1	2	1	0
0065_00025	4	-15	345	1	1	2	1	0
0065_00026	4	7	342	2			0	0
0065_00027	3	-22	350	1	1	2	1	0
0065_00028	4	-14	347	2			0	0
0066_00001	3	1	342	1	1	2	1	0
0066_00002	2	10	178	2			0	0
0066_00003	3	6	336	1			0	0
0067_00001	6	0	511	1	1	2	1	0
0067_00002	5	-3	508	2			0	0
0067_00003	6	0	507	2			0	0
0067_00004	7	-70	503	1	1	1	1	1
0067_00005	5	-1	337	2			0	0
0067_00006	5	1	340	1			0	0
0067_00007	4	1	259	2	1	2	1	0
0067_00008	5	0	345	2			0	0
0067_00009	4	1	260	1	1	2	1	0
0068_00001	8	-25	512	1	1	2	1	0
0068_00002	6	-121	512	1	1	2	1	0
0068_00003	6	2	514	1	1	2	1	0
0068_00004	6	3	505	1	1	1	1	1
0068_00005	4	-18	365	2			0	0
0068_00006	6	-16	545	2			0	0
0068_00007	4	-6	297	2			0	0
0068_00009	2	-20	344	1			0	0
0068_00010	5	-18	351	1			0	0
0068_00011	5	-23	440	1			0	0
0068_00012	5	-67	354	2			0	0
0068_00013	4	-26	334	1	1	2	1	0
0068_00014	5	-20	399	2			0	0
0068_00015	5	-17	358	2	1	2	1	0
0068_00016	2	-17	93	1			0	0
0068_00017	5	-10	385	2	1	2	1	0
0068_00018	4	-13	373	1			0	0
0068_00019	5	1	344	1	1	1	1	1
0068_00020	5	-17	370	2			0	0
0068_00021	5	-19	342	2			0	0

0068_00022	3	-26	174	1	1	1	1	1
0068_00024	4	-18	330	2			0	0
0068_00025	5	41	377	1			0	0
0068_00027	5	8	352	1	1	2	1	0
0068_00028	4	-1	264	2			0	0
0068_00029	5	7	350	1	1	1	1	1
0069_00001	3	-2	360	2	1	1	1	1
0069_00002	7	1	564	1			0	0
0069_00003	6	0	519	2			0	0
0069_00004	6	-6	505	2			0	0
0069_00005	6	1	504	1	1	2	1	0
0069_00007	3	1	172	2			0	0
0069_00008	4	85	348	1	1	2	1	0
0070_00001	7	-13	521	2			0	0
0070_00002	6	1	490	2			0	0
0070_00003	6	1	502	1	1	2	1	0
0070_00004	6	-9	544	1	1	1	1	1
0070_00005	5	-2	447	2			0	0
0070_00006	6	4	452	2			0	0
0070_00007	5	85	540	1	1	2	1	0
0070_00008	4	1	253	2			0	0
0070_00009	4	1	262	2			0	0
0070_00010	3	-6	170	2			0	0
0070_00011	2	-52	6	2			0	0
0070_00013	3	1	170	1	1	2	1	0
0070_00014	5	-3	346	1	1	1	1	1
0070_00015	4	-4	240	2			0	0
0070_00016	4	-1	364	1	1	1	1	1
0070_00018	2	-4	105	2			0	0
0071_00001	5	-5	350	1			0	0
0071_00002	3	5	174	2			0	0
0072_00001	5	-23	512	1	1	1	1	1
0072_00002	6	-6	524	2	1	2	1	0
0072_00003	5	-21	330	2	1	2	1	0
0072_00004	5	-29	349	1	1	2	1	0
0073_00001	6	-71	509	1	1	1	1	1
0073_00002	6	-12	504	2			0	0
0073_00003	2	12	180	1	1	1	1	1
0073_00004	6	-6	514	2			0	0
0073_00005	6	-90	498	1			0	0
0073_00006	6	-21	506	1	1	1	1	1
0073_00008	5	-9	346	1	1	2	1	0
0073_00009	3	-5	246	2	1	1	1	1
0075_00001	6	1	541	1	1	2	1	0
0075_00002	2	-19	92	2			0	0
0075_00003	5	-27	328	1	1	2	1	0
0075_00004	5	-13	333	2			0	0
0075_00005	5	1	331	2			0	0
0075_00006	5	1	344	2			0	0
0076_00002	3	-13	365	2			0	0
0076_00003	4	-68	311	2			0	0
0076_00004	2	-11	352	1			0	0

0077_00001	6	0	506	1	1	2	1	0
0077_00002	6	2	489	1			0	0
0077_00003	4	87	350	1			0	0
0077_00004	3	-4	157	2			0	0
0096_00001	6	0	481	1			0	0
0096_00002	5	-6	349	2			0	0
0096_00003	5	2	364	2			0	0
0096_00004	5	2	335	2			0	0
0096_00005	4	-9	376	1			0	0
0096_00006	5	4	327	2			0	0
0096_00007	5	-2	316	2			0	0
0096_00008	5	-2	362	1	1	2	1	0
0096_00009	5	0	355	2			0	0
0097_00001	5	0	330	1	1	1	1	1
0097_00002	6	0	423	1	1	2	1	0
0097_00003	5	-6	356	2			0	0
0097_00004	5	1	344	1	1	1	1	1
0097_00006	3	-13	346	1			0	0
0097_00007	2	-9	180	2			0	0
0097_00008	4	-35	300	1			0	0
0097_00009	4	0	301	2			0	0
0105_00001	4	-18	335	2			0	0
0107_00001	4	1	385	1			0	0
0109_00001	4	1	339	2			0	0
0115_00001	6	-5	506	1	1	2	1	0
0115_00002	6	-5	513	2			0	0
0115_00003	6	-3	492	2			0	0
0115_00004	6	-12	500	2			0	0
0115_00005	6	-2	531	1	1	2	1	0
0115_00006	5	-3	520	1	1	2	1	0
0115_00007	5	1	435	2			0	0
0115_00008	5	-7	343	1	1	2	1	0
0115_00009	5	0	357	1	1	1	1	1
0115_00010	5	-5	337	2			0	0
0115_00011	5	-13	352	1	1	2	1	0
0115_00012	5	1	360	1	1	2	1	0
0115_00013	5	1	374	1	1	1	1	1
0115_00014	5	-4	368	2			0	0
0115_00015	4	-4	331	2			0	0
0115_00016	4	-4	276	1	1	2	1	0
0115_00017	5	-1	352	1	1	2	1	0
0115_00018	5	-1	331	2			0	0
0116_00001	2	-6	344	2	1	1	1	1
0117_00001	3	179	340	2			0	0
0117_00002	5	-2	361	2			0	0
0117_00003	4	-2	348	1			0	0
0117_00004	3	-6	189	2			0	0
0117_00005	3	-7	182	2			0	0
0117_00006	3	-20	336	1			0	0
0117_00007	5	-20	329	2			0	0
0117_00008	5	6	356	1	1	2	1	0
0117_00009	4	-7	266	1	1	2	1	0

0118_00001	4	-10	337	1			0	0
0118_00002	2	85	252	2			0	0
0119_00001	5	0	337	2			0	0
0119_00002	4	0	347	2			0	0
0120_00001	6	-1	509	1	1	2	1	0
0120_00002	5	-1	349	2	1	2	1	0
0120_00003	5	-14	344	1	1	1	1	1
0120_00005	5	-5	351	1	1	1	1	1
0120_00006	5	1	337	1			0	0
0121_00001	6	6	429	2			0	0
0122_00001	2	170	345	2	1	1	1	1
0122_00002	5	0	355	1	1	1	1	1
0122_00003	4	-2	281	2			0	0
0122_00004	4	-4	429	1			0	0
0122_00005	4	0	260	2			0	0
0122_00006	4	-2	341	1			0	0
0123_00001	6	-2	507	1	1	2	1	0
0123_00002	6	0	510	2			0	0
0123_00003	6	0	511	1	1	2	1	0
0123_00004	5	-4	339	2			0	0
0123_00005	4	-15	342	1	1	1	1	1
0123_00006	5	-16	342	1			0	0
0123_00007	5	-18	345	1	1	2	1	0
0123_00008	5	-6	344	2			0	0
0125_00001	5	-3	387	2			0	0
0125_00002	4	1	261	1			0	0
0125_00003	4	0	340	2			0	0
0126_00001	5	-3	358	2			0	0
0127_00001	4	-6	364	1			0	0
0127_00002	5	1	378	2			0	0
0129_00001	5	1	341	1			0	0
0130_00001	5	-3	415	1			0	0
0131_00001	5	1	345	1			0	0
0131_00002	5	1	343	2			0	0
0131_00003	3	-2	175	1			0	0
0131_00004	5	0	343	1	1	2	1	0
0132_00001	5	1	423	2			0	0
0132_00002	4	-2	337	2			0	0
0132_00003	5	-2	341	2			0	0
0133_00001	5	-1	342	1			0	0
0133_00002	4	0	366	2			0	0
0135_00001	5	-2	370	2			0	0
0135_00002	5	0	351	2			0	0
0135_00003	5	-1	342	1	1	2	1	0
0136_00001	5	1	344	1			0	0
0136_00002	4	1	265	2			0	0
0136_00003	4	-1	249	2			0	0
0137_00001	4	1	272	1	1	1	1	1
0141_00002	5	-6	519	1	1	2	1	0
0141_00003	6	-6	498	2			0	0
0141_00004	6	-4	507	1	1	2	1	0
0141_00005	4	-7	350	2			0	0

0141_00006	3	3	143	2			0	0
0141_00007	5	-5	338	2			0	0
0141_00008	4	-6	253	1			0	0
0141_00009	3	-7	246	1	1	1	1	1
0141_00010	5	-7	337	1			0	0
0141_00011	6	-6	414	1			0	0
0141_00012	4	-6	337	2			0	0
0141_00013	3	-6	344	2			0	0
0141_00014	3	-4	255	2			0	0
0141_00015	5	-6	338	1	1	2	1	0
0141_00016	3	-14	105	2			0	0
0141_00017	4	-6	351	1			0	0
0141_00018	4	-6	351	2			0	0
0141_00019	5	-6	358	1	1	1	1	1
0141_00020	5	-6	349	2			0	0
0141_00021	4	-2	262	1	1	1	1	1
0142_00001	5	1	508	1	1	2	1	0
0142_00002	2	1	342	2			0	0
0142_00003	5	1	533	1	1	2	1	0
0142_00005	4	1	344	1			0	0
0142_00006	3	1	266	1			0	0
0142_00007	4	-5	336	1	1	1	1	1
0142_00008	5	1	345	2			0	0
0142_00009	4	2	345	2			0	0
0142_00010	5	8	421	2			0	0
0143_00001	6	0	431	2			0	0
0143_00002	4	1	246	1			0	0
0143_00003	5	1	337	2			0	0
0143_00004	4	0	367	2			0	0
0143_00005	4	-1	295	2			0	0
0144_00001	4	1	500	2			0	0
0144_00002	2	-6	507	2	1	1	1	1
0144_00003	3	-8	189	2			0	0
0144_00005	5	-8	329	2			0	0
0144_00006	3	-43	350	2	1	2	1	0
0146_00002	5	1	348	1	1	2	1	0
0147_00001	6	0	505	2			0	0
0147_00002	3	-4	353	2			0	0
0147_00003	2	-4	87	2			0	0
0147_00004	4	1	351	2			0	0
0147_00005	3	-2	257	1	1	1	1	1
0147_00006	5	1	337	2			0	0
0148_00001	4	-4	259	1	1	2	1	0
0148_00002	5	-4	344	2			0	0
0148_00003	5	-4	505	2			0	0
0148_00004	4	-1	287	1			0	0
0148_00005	5	-3	341	1	1	2	1	0
0148_00006	4	-6	366	1	1	2	1	0
0148_00007	5	1	342	1	1	2	1	0
0148_00009	5	1	345	1	1	2	1	0
0149_00001	5	-4	506	2			0	0
0149_00002	6	-4	507	2			0	0

0149_00003	6	-4	507	1			0	0
0149_00004	5	-1	335	1	1	1	1	1
0149_00005	5	-1	349	2			0	0
0149_00006	5	-5	339	1	1	2	1	0
0150_00001	6	0	521	2			0	0
0150_00002	4	0	333	2			0	0
0150_00003	4	0	269	2			0	0
0150_00004	5	1	344	1	1	1	1	1
0150_00005	5	1	341	2			0	0
0150_00006	5	0	343	1			0	0
0150_00007	5	1	354	1			0	0
0150_00008	5	1	330	1			0	0
0151_00001	4	1	337	1			0	0
0151_00002	5	95	515	1	1	2	1	0
0151_00003	5	-3	357	1	1	2	1	0
0151_00004	5	-10	343	1			0	0
0151_00005	4	99	354	2			0	0
0151_00006	5	6	347	1	1	2	1	0
0151_00007	3	-3	179	2			0	0
0152_00001	5	-3	474	2			0	0
0152_00002	6	-8	502	1			0	0
0152_00003	5	-3	501	1			0	0
0152_00004	5	-10	512	1	1	2	1	0
0152_00006	5	-4	343	1			0	0
0152_00007	5	-4	343	2			0	0
0152_00008	5	-2	313	2			0	0
0152_00009	4	-6	182	2			0	0
0152_00010	5	-1	342	2			0	0
0152_00011	2	90	174	1	1	2	1	0
0153_00001	6	-5	517	1			0	0
0153_00002	6	-3	515	1			0	0
0153_00003	6	-3	515	1	1	1	1	1
0153_00004	5	-3	354	1			0	0
0153_00005	5	-3	340	2			0	0
0153_00006	4	-4	360	2			0	0
0153_00007	3	-2	347	1	1	1	1	1
0153_00008	5	-3	340	1			0	0
0154_00001	5	-4	339	1			0	0
0154_00002	4	-4	339	1	1	1	1	1
0154_00003	5	-4	339	1	1	1	1	1
0154_00004	3	1	336	2			0	0
0154_00005	4	1	252	1	1	2	1	0
0155_00001	5	2	513	1			0	0
0155_00002	2	-12	94	2			0	0
0155_00003	6	-3	512	2			0	0
0155_00004	5	-4	374	1			0	0
0155_00005	5	6	358	1	1	1	1	1
0155_00007	3	6	200	2			0	0
0155_00008	5	4	354	1	1	1	1	1
0155_00009	4	1	258	2			0	0
0156_00001	2	1	86	2			0	0
0156_00002	5	0	364	2			0	0

0157_00002	6	1	497	1			0	0
0157_00003	3	1	189	2			0	0
0157_00004	5	-40	350	1			0	0
0157_00005	5	-8	348	1	1	1	1	1
0158_00001	3	0	512	2			0	0
0158_00002	6	-2	508	2			0	0
0158_00003	3	-1	344	2	1	2	1	0
0158_00004	3	-5	358	2			0	0
0159_00001	6	-1	505	1			0	0
0159_00002	5	1	339	2			0	0
0159_00003	5	1	324	1	1	1	1	1
0159_00004	4	0	337	1	1	2	1	0
0160_00001	6	1	508	2			0	0
0160_00002	6	-4	514	2			0	0
0160_00003	4	-2	253	1			0	0
0160_00004	3	-6	250	1	1	2	1	0
0160_00005	2	86	169	2			0	0
0160_00006	3	-10	331	1	1	1	1	1
0160_00007	4	0	337	2			0	0
0160_00008	3	-4	164	2			0	0
0160_00009	3	-5	176	2			0	0
0160_00010	5	-5	338	2			0	0
0161_00001	6	0	510	1	1	2	1	0
0161_00002	2	0	187	2			0	0
0161_00003	7	1	529	2			0	0
0161_00004	2	-6	102	1			0	0
0161_00005	5	1	367	1	1	2	1	0
0161_00006	5	1	351	1			0	0
0163_00001	6	1	546	1	1	1	1	1
0163_00002	6	1	525	1			0	0
0163_00003	2	1	98	2			0	0
0163_00004	2	1	103	2			0	0
0164_00001	4	-1	338	1	1	1	1	1
0164_00002	4	-1	338	2			0	0
0164_00004	2	-5	255	2			0	0
0164_00005	4	0	254	2			0	0
0164_00006	3	0	350	1	1	2	1	0
0164_00007	3	0	345	2			0	0
0164_00008	4	0	343	2			0	0
0165_00001	2	-5	174	2			0	0
0165_00002	5	-7	349	1	1	2	1	0
0165_00003	3	-8	343	1	1	2	1	0
0165_00004	4	1	346	1	1	2	1	0
0165_00005	2	0	266	2	1	1	1	1
0166_00001	2	0	174	2			0	0
0166_00002	3	0	350	1			0	0
0167_00001	6	-6	475	2			0	0
0167_00002	5	-7	345	1			0	0
0167_00003	5	-6	344	1	1	2	1	0
0168_00002	4	-1	221	1			0	0
0170_00001	2	0	100	2			0	0
0170_00003	3	-5	349	1			0	0

0170_00004	5	0	337	1	1	2	1	0
0170_00005	4	-6	263	1	1	1	1	1
0170_00006	4	1	312	2			0	0
0171_00001	6	1	504	1	1	2	1	0
0181_00001	6	-2	503	2			0	0
0181_00002	6	0	509	1	1	2	1	0
0181_00003	5	-2	509	1	1	1	1	1
0181_00004	6	-2	518	1	1	2	1	0
0181_00005	6	-2	517	2			0	0
0181_00006	5	-5	338	1	1	2	1	0
0181_00007	5	-24	338	2			0	0
0181_00008	5	-6	338	2			0	0
0701_00001	4	0	354	1			0	0
0701_00002	5	-2	358	1	1	2	1	0
0701_00003	5	1	339	1	1	2	1	0
0701_00004	2	-2	91	2			0	0
0701_00005	2	0	91	2			0	0
0701_00006	2	-2	86	2			0	0
0701_00007	2	1	60	2			0	0
0702_00002	3	-2	337	2			0	0
0703_00001	4	-1	341	1			0	0
0703_00002	4	-2	340	1	1	2	1	0
0705_00001	4	-5	254	1			0	0
0705_00002	5	-5	338	1	1	2	1	0
0705_00003	5	-5	387	2			0	0
0705_00004	5	-5	338	1			0	0
0705_00005	3	-5	184	2			0	0
0705_00006	4	0	338	2			0	0
0705_00007	4	0	259	1	1	2	1	0
0705_00008	4	90	341	1	1	1	1	1
0705_00009	3	92	260	1			0	0
0706_00001	5	-6	339	1	1	1	1	1
0706_00003	5	1	352	2			0	0
0706_00004	4	-2	347	2	1	1	1	1
0706_00005	5	0	354	1	1	1	1	1
0710_00001	5	1	337	1			0	0
0710_00004	5	-101	347	1	1	2	1	0
0713_00001	2	95	341	2			0	0
0713_00002	2	-2	123	2			0	0
0713_00003	5	-4	514	2	1	2	1	0
0713_00004	5	1	337	1	1	2	1	0
0713_00005	3	1	180	2			0	0
0713_00006	5	1	348	1			0	0
0713_00007	2	90	174	2			0	0
0713_00008	5	-3	338	1	1	2	1	0
0714_00001	5	-2	502	1	1	2	1	0
0714_00002	2	-4	182	1			0	0
0714_00003	4	-2	376	2			0	0
0714_00004	4	0	351	2			0	0
0714_00006	4	-6	320	1			0	0
0714_00007	5	-5	373	2			0	0
0714_00008	2	-6	93	1	1	1	1	1

0714_00009	3	1	174	1	1	2	1	0
0714_00010	5	-3	343	1			0	0
0714_00011	6	-2	453	2			0	0
0714_00012	3	-5	172	1	1	2	1	0
0714_00013	2	-6	95	2			0	0
0714_00014	5	0	379	1	1	2	1	0
0714_00015	4	-6	348	1			0	0
0714_00016	5	-5	349	1			0	0
0714_00017	5	-3	350	2	1	2	1	0
0716_00001	4	1	344	2	1	2	1	0
0716_00002	4	1	268	1	1	2	1	0
0716_00003	4	-12	352	1			0	0
0716_00004	3	-4	352	2			0	0
0717_00001	5	-5	343	2			0	0
0717_00002	4	-3	345	2			0	0
0717_00004	4	-4	352	1			0	0
0717_00005	2	-6	258	2	1	1	1	1
0717_00006	5	-4	339	1	1	2	1	0
0717_00007	5	1	357	2			0	0
0717_00008	5	7	342	2			0	0
0717_00010	4	2	338	2			0	0
0717_00012	4	90	356	1	1	2	1	0
0718_00002	4	-2	271	1	1	1	1	1
0718_00003	3	-2	253	2			0	0
0718_00004	3	1	256	2			0	0
0719_00001	2	1	191	2			0	0
0719_00002	4	1	338	2			0	0
0719_00003	4	1	337	1			0	0
0719_00004	2	1	81	2			0	0
0720_00001	5	1	348	2	1	2	1	0
0720_00002	3	1	173	2			0	0
0720_00003	5	0	354	1			0	0
0720_00004	2	1	88	2			0	0
0720_00005	4	-3	350	2			0	0
0720_00006	3	1	343	1	1	1	1	1
0720_00008	5	-4	343	2			0	0
0721_00001	3	-7	259	2	1	2	1	0
0721_00002	2	1	95	1			0	0
0722_00001	5	1	338	1	1	1	1	1
0722_00002	4	1	331	1	1	2	1	0
0722_00003	2	1	181	2			0	0
0722_00004	4	1	244	1	1	2	1	0
0722_00005	4	1	352	1			0	0
0722_00006	4	1	358	1	1	2	1	0
0723_00001	5	-2	341	1			0	0
0723_00002	5	-6	339	2			0	0
0724_00002	3	88	253	1	1	1	1	1
0724_00003	3	173	348	1	1	2	1	0
0724_00004	4	0	339	1			0	0
0726_00002	3	-9	252	1	1	1	1	1
0726_00003	5	-6	351	1			0	0
0726_00005	5	-3	347	1	1	1	1	1

0726_00006	3	170	296	1			0	0
0726_00007	3	-3	353	2			0	0
0726_00008	4	2	341	1	1	2	1	0
0726_00009	5	-10	347	1	1	1	1	1
0726_00010	5	-1	345	1			0	0
0727_00001	4	-4	349	2			0	0
0727_00002	5	-4	345	1			0	0
0727_00003	5	-6	349	2			0	0
0727_00005	4	-6	257	1			0	0
0727_00006	4	11	354	2			0	0
0727_00007	5	-1	349	2			0	0
0727_00008	2	-6	90	2			0	0
0727_00009	2	0	89	1			0	0
0727_00010	4	-6	338	2			0	0
0727_00011	3	1	185	2			0	0
0727_00012	5	-5	345	1	1	1	1	1
0727_00013	2	92	260	2			0	0
0727_00014	5	1	348	2			0	0
0728_00001	3	-1	174	2			0	0
0728_00002	5	-6	343	1	1	1	1	1
0728_00003	5	0	336	2			0	0
0728_00004	5	-1	341	1			0	0
0728_00005	5	-1	351	1	1	2	1	0
0729_00005	4	-3	250	1			0	0
0729_00006	5	0	356	2	1	2	1	0
0731_00001	4	-78	258	2			0	0
0732_00001	5	1	346	2			0	0
0732_00002	5	1	330	1			0	0
0732_00003	4	1	336	1			0	0
0732_00004	4	1	309	2			0	0
0732_00005	5	1	344	2			0	0
0732_00006	5	1	339	2			0	0
0733_00001	5	10	346	1	1	2	1	0
0733_00002	2	0	91	2			0	0
0735_00001	5	-9	348	2			0	0
0735_00002	3	-2	182	2			0	0
0735_00003	2	1	230	2			0	0
0735_00004	4	-10	331	1			0	0
0736_00001	5	-8	302	1			0	0
0736_00002	4	8	347	1			0	0
0737_00001	3	1	164	2			0	0
0737_00002	5	1	301	1			0	0
0737_00003	5	1	330	1			0	0
0737_00004	5	1	337	2			0	0
0737_00005	4	1	343	2	1	1	1	1
0737_00007	5	1	344	2			0	0
0737_00008	4	1	351	1	1	2	1	0
0737_00009	5	-4	351	1			0	0
0737_00010	2	1	85	2			0	0
0737_00011	5	-15	342	1	1	1	1	1
0737_00013	4	-4	255	1			0	0
0737_00014	3	1	270	1	1	2	1	0

0738_00001	4	1	344	1			0	0
0738_00002	3	2	390	2			0	0
0738_00003	4	-9	255	2			0	0
0738_00004	5	-6	358	1			0	0
0738_00005	4	1	380	2	1	1	1	1
0738_00006	5	-2	350	1	1	1	1	1
0738_00007	5	-2	348	2			0	0
0738_00008	4	-2	348	1			0	0
0738_00009	5	-6	358	1	1	2	1	0
0738_00011	5	1	344	2			0	0
0738_00012	5	3	360	2			0	0
0738_00013	4	-8	352	1	1	1	1	1
0738_00014	2	-6	110	2			0	0
0738_00015	6	-5	403	2			0	0
0738_00016	2	1	180	2			0	0
0738_00017	5	-5	337	1	1	2	1	0
0738_00018	4	1	344	2			0	0
0738_00019	5	1	353	2			0	0
0739_00001	3	3	179	1			0	0
0739_00002	3	1	176	2	1	1	1	1
0739_00003	4	-7	264	2			0	0
0741_00001	4	113	367	1	1	1	1	1
0741_00002	4	-5	346	2			0	0
0741_00003	5	-18	339	1			0	0
0741_00004	5	-6	343	1			0	0
0741_00005	5	-4	342	1			0	0
0742_00001	4	1	354	2			0	0
0742_00002	5	-9	342	1	1	2	1	0
0742_00003	3	-7	257	1	1	1	1	1
0742_00004	6	-6	339	1			0	0
0743_00001	5	-2	340	1	1	1	1	1
0743_00002	5	-6	344	1			0	0
0743_00003	5	-3	328	1	1	1	1	1
0744_00001	5	-3	378	1			0	0
0744_00002	5	-5	330	1			0	0
0744_00003	5	0	335	2			0	0
0744_00004	3	-5	254	1			0	0
0746_00001	5	-12	352	2			0	0
0746_00002	5	-12	329	1			0	0
0746_00003	3	-1	181	2			0	0
0746_00004	3	-1	133	1			0	0
0747_00001	5	5	341	1	1	1	1	1
0747_00002	5	0	337	2			0	0
0747_00003	5	3	339	1	1	1	1	1
0747_00004	4	86	337	2			0	0
0747_00005	5	0	342	1	1	2	1	0
0747_00006	5	1	344	2			0	0
0748_00001	5	1	336	1			0	0
0749_00001	4	0	346	2			0	0
0750_00001	5	0	342	1	1	2	1	0
0751_00001	2	-6	346	2	1	1	1	1
0751_00002	4	93	355	1	1	2	1	0

0751_00003	3	1	183	1			0	0
0751_00004	2	1	88	1			0	0
0752_00001	5	-7	356	2			0	0
0752_00002	5	1	348	1	1	2	1	0
0752_00003	4	4	267	1			0	0
0753_00002	2	0	121	2			0	0
0755_00001	5	6	349	1	1	1	1	1
0755_00002	5	-1	338	1			0	0
0755_00003	2	-2	95	2			0	0
0755_00004	5	2	337	1	1	1	1	1
0755_00005	5	-5	336	1	1	1	1	1
0755_00006	5	0	372	2			0	0
0755_00007	5	1	346	1	1	1	1	1
0756_00001	6	-8	428	2			0	0
0756_00002	3	-5	264	1	1	2	1	0
0756_00004	4	-7	426	1	1	1	1	1
0756_00005	3	-5	158	2			0	0
0756_00006	5	0	384	2			0	0
0756_00007	2	88	176	1			0	0
0756_00008	4	-5	342	1	1	1	1	1
0756_00009	4	84	336	1	1	2	1	0
0756_00010	3	-5	350	1	1	1	1	1
0756_00011	5	-2	344	1			0	0
0756_00012	2	-6	88	2			0	0
0756_00013	4	-1	344	2			0	0
0756_00014	4	86	344	1	1	2	1	0
0756_00015	4	-1	254	1	1	2	1	0
0756_00016	4	0	266	1	1	2	1	0
0756_00017	4	0	350	2			0	0
0756_00018	4	-22	337	1			0	0
0756_00019	3	-4	178	2			0	0
0756_00020	4	-3	256	1	1	2	1	0
0756_00021	2	-3	172	2			0	0
0757_00001	3	1	551	2	1	1	1	1
0757_00002	4	-1	533	2			0	0
0757_00003	2	1	264	2			0	0
0757_00004	5	1	354	1			0	0
0757_00005	6	1	491	1			0	0
0757_00006	6	1	517	1	1	1	1	1
0757_00007	6	1	507	1	1	1	1	1
0757_00008	5	1	333	2			0	0
0757_00009	6	1	530	1	1	1	1	1
0757_00010	5	1	501	1	1	2	1	0
0757_00011	5	1	528	2			0	0
0757_00012	4	1	353	2			0	0
0757_00013	6	0	541	1	1	2	1	0
0757_00014	4	1	519	1			0	0
0757_00015	5	1	524	1	1	2	1	0
0757_00016	5	1	319	2			0	0
0757_00017	6	1	513	1	1	1	1	1
0757_00018	4	98	512	2			0	0
0757_00019	4	0	252	1	1	1	1	1

0757_00020	4	1	259	2			0	0
0757_00021	5	1	468	2			0	0
0757_00022	3	1	184	2			0	0
0757_00023	4	1	365	1			0	0
0757_00025	5	1	346	1			0	0
0757_00026	5	0	354	2			0	0
0757_00027	3	0	349	2	1	1	1	1
0757_00028	4	1	277	1	1	1	1	1
0757_00029	4	-1	238	2			0	0
0757_00030	3	-1	190	2			0	0
0757_00032	2	1	184	1	1	1	1	1
0757_00034	3	1	174	2			0	0
0757_00035	5	1	382	2			0	0
0757_00036	3	1	191	2			0	0
0757_00037	5	-10	337	1	1	2	1	0
0757_00038	4	-1	381	2			0	0
0757_00039	3	1	349	1			0	0
0757_00040	4	-1	363	1	1	2	1	0
0757_00041	3	1	183	2			0	0
0757_00042	3	-1	344	2	1	2	1	0
0757_00043	4	1	341	2			0	0
0757_00044	2	-1	94	2			0	0
0757_00045	5	-2	369	1	1	1	1	1
0757_00046	4	1	341	1			0	0
0757_00047	5	1	365	1			0	0
0757_00048	3	92	365	2			0	0
0759_00001	4	-8	260	2			0	0
0759_00002	6	-8	414	2			0	0
0759_00003	4	-5	261	2			0	0
0759_00004	5	1	358	2			0	0
0759_00005	5	0	338	2			0	0
0759_00006	4	0	337	2			0	0
0759_00007	4	0	350	1	1	1	1	1
0759_00008	5	-1	344	2			0	0
0759_00009	3	-5	163	2			0	0
0759_00010	5	-5	338	1	1	2	1	0
0759_00011	5	0	344	2			0	0
0759_00012	3	-6	175	2			0	0
0759_00013	2	0	95	2			0	0
0759_00014	5	-2	329	1	1	2	1	0
0759_00015	5	-1	345	1	1	1	1	1
0759_00016	5	1	351	1	1	2	1	0
0759_00017	2	169	253	1	1	2	1	0
0759_00018	4	0	260	1	1	2	1	0
0759_00019	4	-2	264	2			0	0
0759_00020	4	-4	339	1			0	0
0759_00021	5	1	347	1	1	2	1	0
0759_00022	4	-1	260	2	1	2	1	0
0759_00023	2	0	88	1	1	1	1	1
0759_00024	2	-2	93	2			0	0
0761_00001	4	-2	345	1	1	1	1	1
0761_00002	5	-2	338	2			0	0

0761_00003	4	-3	344	1	1	1	1	1
0761_00004	5	-2	363	2			0	0
0761_00005	5	-46	345	2			0	0
0761_00006	5	-3	334	1	1	1	1	1
0761_00007	5	-1	338	2			0	0
0762_00001	5	0	347	1			0	0
0762_00002	2	1	88	1			0	0
0762_00003	3	1	169	1			0	0
0763_00001	4	-3	342	2			0	0
0763_00002	5	0	365	1	1	2	1	0
0763_00003	5	-16	366	2			0	0
0763_00004	5	-5	352	1	1	2	1	0
0763_00005	5	-4	349	1	1	2	1	0
0763_00006	5	-3	343	1	1	1	1	1
0763_00007	4	-4	275	2			0	0
0763_00008	3	-5	177	1	1	2	1	0
0764_00001	4	0	349	1	1	1	1	1
0764_00002	5	-2	343	2			0	0
0764_00003	4	-1	252	1			0	0
0764_00004	4	1	410	1			0	0
0764_00005	5	1	341	1			0	0
0765_00001	6	-6	515	1	1	2	1	0
0765_00002	5	-6	348	2			0	0
0765_00003	4	-5	256	1			0	0
0765_00004	5	-2	340	1	1	1	1	1
0765_00005	5	-1	377	1			0	0
0765_00006	5	0	344	1	1	2	1	0
0765_00007	5	-6	337	1			0	0
0765_00008	5	1	350	2			0	0
0765_00009	5	-6	347	1	1	2	1	0
0765_00010	3	1	176	2			0	0
0765_00011	5	-7	343	1			0	0
0765_00012	2	1	92	2			0	0
0765_00013	2	-2	268	1	1	1	1	1
0765_00014	4	-3	340	1	1	1	1	1
0766_00003	5	-5	351	1	1	1	1	1
0767_00001	2	2	141	2			0	0
0767_00002	4	99	344	1	1	2	1	0
0768_00001	5	1	343	1	1	1	1	1
0769_00001	5	89	509	1	1	2	1	0
0769_00002	4	91	504	1	1	1	1	1
0769_00003	4	87	339	1	1	1	1	1
0769_00004	4	1	342	2	1	2	1	0
0769_00005	2	-7	190	2			0	0
0769_00006	2	100	166	2			0	0
0769_00007	5	0	329	1	1	1	1	1
0769_00008	3	0	266	2			0	0
0769_00009	3	99	344	2			0	0
0769_00011	4	-5	271	2	1	1	1	1
0770_00001	2	-6	170	2			0	0
0770_00002	3	1	344	2			0	0
0770_00003	5	0	344	2			0	0

0771_00001	5	0	378	1			0	0
0771_00002	4	90	384	1			0	0
0771_00003	2	176	365	2			0	0
0771_00004	5	0	350	1			0	0
0771_00005	5	0	365	1			0	0
0771_00006	2	-1	111	2			0	0
0771_00007	5	0	365	1			0	0
0771_00008	5	0	351	1			0	0
0771_00009	5	1	411	1			0	0
0771_00010	5	-4	372	1			0	0
0771_00011	5	-4	386	1	1	2	1	0
0771_00013	3	0	317	1			0	0
0771_00014	5	-5	359	1			0	0
0771_00015	5	-3	374	1			0	0
0771_00016	3	-4	180	2			0	0
0771_00017	5	0	368	2			0	0
0771_00018	5	-3	375	2			0	0
0771_00019	2	-4	285	2			0	0
0771_00020	2	1	114	2			0	0
0774_00001	4	0	360	1	1	1	1	1
0774_00002	3	-5	337	2	1	2	1	0
0774_00003	4	-2	299	1	1	2	1	0
0774_00004	2	269	353	1	1	1	1	1
0774_00005	5	-7	350	2			0	0
0775_00001	3	-2	173	2			0	0
0775_00004	2	-2	96	1			0	0
0776_00001	4	95	340	1	1	1	1	1
0776_00002	3	-97	84	2			0	0
0776_00003	4	-2	345	1	1	1	1	1
0776_00004	4	-2	261	1			0	0
0776_00005	3	1	345	1	1	1	1	1
0777_00001	2	0	94	2			0	0
0777_00002	2	0	93	2			0	0
0777_00003	2	0	91	2			0	0
0778_00001	5	-1	342	2			0	0
0778_00002	5	-27	272	1	1	2	1	0

Staten, Ann M

From: Staten, Ann M
Sent: Thursday, November 14, 2002 9:43 AM
To: Robert Miranda (E-mail)
Subject: Gleevec S-004 question - clinical

Importance: High

Dear Bob,

We have the following additional question from the medical reviewer.

Why were these bone marrow cytogenetic results not considered to be consistent with complete cytogenetic responses (KR's)?


Gleevec CyR's.pdf


Gleevec CyR's xls

Thanks,

Ann

SID1A	FISH	KR	PHPOS1N	STDDAY
0017_00001	0	6	.	169
0018_00008	.	2	0	350
0028_00003	0	6	.	92
0028_00006	.	2	0	114
0028_00007	.	6	0	364
0029_00004	.	2	0	115
0029_00004		2	0	332
0029_00004	.	6	0	416
0029_00004	.	6	0	500
0048_00006	.	6	0	258
0048_00011	.	6	0	331
0051_00007	.	6	0	260
0054_00009	.	6	0	337
0065_00002	.	2	0	173
0067_00007	.	2	0	175
0067_00007	.	6	0	259
0068_00010	.	6	0	260
0068_00010	.	6	0	351
0068_00014	.	6	0	261
0072_00003	.	2	0	253
0072_00003	.	6	0	330
0073_00003	.	6	0	180
0073_00004	.	6	0	339
0073_00004	.	6	0	514
0073_00005	.	6	0	170
0073_00005	.	2	0	253
0073_00006	.	2	0	253
0073_00008	.	2	0	172
0097_00001	.	2	0	330
0115_00006	.	2	0	254
0115_00006	.	6	0	520
0135_00001	.	6	0	264
0144_00002	.	6	0	507
0144_00006	.	6	0	350
0160_00007	.	6	0	337
0160_00010	.	6	0	338
0163_00001	.	2	0	97
0164_00006	.	6	0	350
0164_00007	.	6	0	345
0167_00001	.	6	0	177
0167_00001	.	6	0	260
0167_00001	.	6	0	344
0167_00001	.	6	0	475
0167_00002	.	6	0	260
0167_00002	.	6	0	345
0714_00008	.	6	0	93
0717_00002	.	6	0	345
0726_00007	.	6	0	353
0726_00008	.	2	0	187
0742_00003	.	2	0	89
0755_00005	.	6	0	84

0755_00005	.	2	0	168
0759_00014	.	2	0	169
0759_00014	.	6	0	252
0759_00014	.	6	0	329
0759_00018	.	2	0	88
0765_00005	.	2	0	188
0765_00006	.	2	0	260
0771_00004		6	0	350
0771_00005	.	6	0	96
0771_00014	.	2	0	359

SID1A	FISH	KR	PHPOS1N	STDDAY
0017_00001	0	6	.	169
0018_00008	.	2	0	350
0028_00003	0	6	.	92
0028_00006	.	2	0	114
0028_00007	.	6	0	364
0029_00004	.	2	0	115
0029_00004	.	2	0	332
0029_00004	.	6	0	416
0029_00004	.	6	0	500
0048_00006	.	6	0	258
0048_00011	.	6	0	331
0051_00007	.	6	0	260
0054_00009	.	6	0	337
0065_00002	.	2	0	173
0067_00007	.	2	0	175
0067_00007	.	6	0	259
0068_00010	.	6	0	260
0068_00010	.	6	0	351
0068_00014	.	6	0	261
0072_00003	.	2	0	253
0072_00003	.	6	0	330
0073_00003	.	6	0	180
0073_00004	.	6	0	339
0073_00004	.	6	0	514
0073_00005	.	6	0	170
0073_00005	.	2	0	253
0073_00006	.	2	0	253
0073_00008	.	2	0	172
0097_00001	.	2	0	330
0115_00006	.	2	0	254
0115_00006	.	6	0	520
0135_00001	.	6	0	264
0144_00002	.	6	0	507
0144_00006	.	6	0	350
0160_00007	.	6	0	337
0160_00010	.	6	0	338
0163_00001	.	2	0	97
0164_00006	.	6	0	350
0164_00007	.	6	0	345
0167_00001	.	6	0	177
0167_00001	.	6	0	260
0167_00001	.	6	0	344
0167_00001	.	6	0	475
0167_00002	.	6	0	260
0167_00002	.	6	0	345
0714_00008	.	6	0	93
0717_00002	.	6	0	345
0726_00007	.	6	0	353
0726_00008	.	2	0	187
0742_00003	.	2	0	89
0755_00005	.	6	0	84

0755_00005	.	2	0	168
0759_00014	.	2	0	169
0759_00014	.	6	0	252
0759_00014	.	6	0	329
0759_00018	.	2	0	88
0765_00005	.	2	0	188
0765_00006	.	2	0	260
0771_00004	.	6	0	350
0771_00005	.	6	0	96
0771_00014	.	2	0	359

Redacted 6

pages of trade

secret and/or

confidential

commercial

information

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Monday, November 11, 2002 8:14 AM
To: statena@cder.fda.gov
Subject: Response to Review Questions of 11/7/02 (Table 9-17)

Importance: High


110702 FDA Review Questions (t..


111102 Response to FDA Questio...

Hi Ann,

Attached is our response to the reviewer's questions received via secure e-mail on Nov 7, 2002, as well as by fax on Nov 8, 2002. This concerned Table 9-17 from page 96 of the study report.

Please note that in Table 9-17 the top portion shows the initial events for
TTP (summarizing patients' first event type), whereas the last line shows
the events of AP/BC (in which patients can be included who progressed initially for other reason and then subsequently progressed to AP/BC).

Please find attached a detailed listing and explanation how we counted the
events for TTP and Time to AP/BC (and where the differences are).

I hope this provides the clarification needed and that we can agree on the
numbers. Please let me know if you have any further questions.

Thanks
Bob.....

(See attached file: 110702 FDA Review Questions (table 9-17).pdf)
(See attached file: 111102 Response to FDA Questions (table 9-17).doc)

973. 781. 5217

COPIED KEVIN

FDA QUERY Nov 7, 2002

Table 9-17 P 96 from study report

	STI571 N=553 (%)	IFN+Ara-C N=553 (%)
Total no. of patients with events (progression)	**24 (4.3)**	**103 (18.6)**
Progression to accelerated phase or blast crisis	8 (1.4)	32 (5.8)
Loss of CHR	6 (1.1)	39 (7.1)
Loss of MCyR	4 (0.7)	6 (1.1)
Increase in WBC (approved by SMC)	2 (0.4)	24 (4.3)
Death during treatment	4 (0.7)	2 (0.4)
Total no.of patients with progression to AP or BC	**10 (1.8)**	**36 (6.5)**

From eff 1st and eff 2nd datasets

	Gleevec N=553 (%)	IFN+Ara-C N=553 (%)
Progression to accelerated phase ACCEL_N	10 (1.8)	36 (5.8)
Loss of CHR LCHRDT_N	6 (1.1)	37 (6.5)
Loss of MCyR* LODTMKR	7 (1.2)	8 (1.4)
Increase in WBC INCDT_N	2 (0.4)	25 (4.5)
Death during treatment REASON = 10	4 (0.7)	2 (0.4)
Total no. of patients with events (progression)	**29 (5.2)**	**108 (19.5)**

* 6 patients also had other reason for of CHR, 4 on gleevec and 2 on IFN

Please explain the minor differences between the study report summary of progression events and the results derived from the EFF 1st and 2nd datasets.

In Table 9-17, what was the reason for the 2 different numbers for progression to accelerated phase events? Was the top line summarizing AP events that were counted as initial progressions and the bottom line also included pts that progressed for other reasons and subsequently also progressed into AP?

Study 106 - TTP events

---------- Randomization treatment = STI571 ----------

Obs	Patient	Progression to AP/BC	Loss of CHR	Loss of MCyR	Increase in WBC	Death during treatment
1	0003_00003	19SEP2000				.
2	0026_00003	19NOV2001	19NOV2001	05NOV2001		.
3	0048_00004	07AUG2001	07AUG2001	07AUG2001		.
4	0077_00002	21JAN2002	21JAN2002	21JAN2002	.	.
5	0142_00004	06OCT2000	.	.		.
6	0727_00009	05FEB2001		.	.	.
7	0737_00002	08AUG2001	08AUG2001		.	.
8	0746_00004	06JUN2001	06JUN2001	06JUN2001		.
9	0756_00007	05MAY2001	.	.	12APR2001	.
10	0762_00003	26MAR2001	26MAR2001	.	.	.
11	0046_00002		19DEC2001			.
12	0097_00006	.	22AUG2001	.		.
13	0151_00004		15OCT2001		.	
14	0154_00001		30NOV2001	.		.
15	0716_00003		26APR2001			.
16	0738_00008	.	29NOV2001	.	.	.
17	0069_00002	.	.	06NOV2001		
18	0727_00002		.	25MAY2001	.	
19	0742_00004	.	.	17JUL2001	.	.
20	0148_00004	.	.	.	13SEP2001	.
21	0016_00002	.	.	.		03MAR2001
22	0050_00004			.		16JAN2002
23	0159_00003	.	.		.	06JAN2002
24	0765_00003		.		.	03AUG2001

The summary of events on STI571 (based on ITT) is as follows (explanation on Table 9-17 is underlined):

- 10 progressions to AP/BC (in Table 9-17 two of these patients were listed as 'Loss of MCyR' and 'Increase in WBC' respectively as these were the patients' first events)
- 6 loss CHR (another 6 patients lost CHR and progressed to AP/BC at the same time, therefore were counted as AP/BC)
- 3 loss MCyR (another 3 patients lost MCyR and progressed to AP/BC at the same time, therefore were counted as AP/BC + one patient had lost MCyR on first-line and then progressed to AP/BC on second-line >>> now counted as AP/BC but included in Table 9-17 as 'Loss MCyR')
- 1 increase in WBC (one patient had increased WBC on first-line and then progressed to AP/BC on second-line >> now counted as AP/BC but included in Table 9-17 as 'Increase in WBC')
- 4 patients died during treatment

Therefore in the table derived from eff 1st and eff 2nd datasets, the 3 patients with loss of MCyR (but AP/BC at the same time, see above listing) need to be subtracted, as well as the two patients who had event on first-line (one 'Loss MCyR' and one 'Increase in WBC') and then progressed to AP/BC during second-line:

29 events - 3 loss MCyR - 1 loss MCyR - 1 increase in WBC = 24 events

Or alternatively (to get Table 9-17) delete only the 3 loss MCyR and list the other two patients with their first event, i.e. delete two AP/BC.

---------- Randomization treatment = IFN+Ara-C ----------

Obs	Patient	Progression to AP/BC	Loss of CHR	Loss of MCyR	Increase in WBC	Death during treatment
25	0006_00004	18NOV2001	18NOV2001	18NOV2001	.	.
26	0032_00001	18OCT2000	.	.	.	.
27	0033_00006	24JUN2001	24JUN2001		.	.
28	0035_00001	02MAY2001	02MAY2001	.	.	.
29	0054_00008	11APR2001	07MAR2001	.	.	.
30	0065_00012	10MAY2001	10MAY2001	10MAY2001	.	.
31	0065_00017	22NOV2000	.	.	.	
32	0068_00007	16MAY2001		.	.	

33	0068_00028	03DEC2001	03DEC2001			
34	0070_00018	18OCT2001	18OCT2001			
35	0073_00007	08DEC2000				
36	0075_00002	28SEP2000				
37	0076_00001	04AUG2000				
38	0117_00005	12AUG2001	12AUG2001			
39	0142_00002	22NOV2001	22AUG2001			
40	0147_00002	17SEP2001	17SEP2001			
41	0147_00003	03JAN2001	03JAN2001			
42	0148_00008	04FEB2001				
43	0152_00008	17SEP2001	20AUG2001			
44	0152_00009	26APR2001	26APR2001	26APR2001		
45	0155_00002	19OCT2000				
46	0155_00006	27NOV2000				
47	0156_00001	17JAN2001				
48	0165_00001	13MAR2001				
49	0166_00001	11JUL2001				
50	0701_00007	18MAR2001				
51	0714_00013	24JAN2001	24JAN2001			
52	0726_00001	10NOV2000				
53	0727_00013	30SEP2001				
54	0732_00004	11OCT2001	11OCT2001			
55	0735_00003	20JUN2001				
56	0738_00015	27DEC2001	26NOV2001			
57	0738_00016	06FEB2001				
58	0756_00005	13FEB2001				
59	0766_00001	31AUG2001				
60	0770_00001	26JUL2001	26JUL2001			
61	0002_00002		27SEP2001			
62	0003_00001		26FEB2001			
63	0004_00002		25OCT2001			
64	0011_00002		07AUG2001			
65	0018_00006		31MAY2001			
66	0020_00003		22NOV2001			
67	0031_00001		14NOV2000			
68	0046_00004		16JUL2001			
69	0050_00002		12FEB2001			
70	0051_00006		20AUG2001			
71	0054_00009		29JAN2001			
72	0065_00023		05DEC2001			
73	0067_00008		07JUN2001			
74	0069_00004		21NOV2000			
75	0070_00006		05MAR2001			
76	0075_00006		31AUG2001			
77	0076_00002		19JUN2001			
78	0115_00018		08NOV2001			
79	0132_00001		18JUN2001		02OCT2001	
80	0141_00014		27JUN2001			
81	0153_00005		22OCT2001		20DEC2001	
82	0157_00003		02APR2001			
83	0160_00001		18APR2001			
84	0160_00002		14MAR2001			
85	0164_00004		20NOV2001			
86	0706_00003		10JUL2001		14AUG2001	
87	0714_00004		26DEC2001			
88	0717_00008		19SEP2001			
89	0717_00010		14DEC2001			
90	0727_00008		16JUL2001			
91	0738_00018		28MAR2001			
92	0757_00018		06DEC2000			
93	0757_00026		25JUN2001			
94	0757_00038		09AUG2001		09AUG2001	
95	0778_00001		19NOV2001			
96	0036_00005			19JUL2001		
97	0050_00003			23JAN2002		
98	0135_00001			26FEB2001		
99	0181_00008			02OCT2001		
100	0717_00001			03JUL2001		
101	0757_00020			15FEB2001		
102	0002_00009				26AUG2001	
103	0030_00003				06JUN2001	

104	0030_00004	12NOV2001	
105	0033_00002	05JUN2001	
106	0061_00001	22NOV2001	
107	0071_00002	29MAY2001	
108	0115_00007	19MAR2001	
109	0133_00002	08MAY2001	
110	0136_00002	22OCT2001	
111	0164_00007	23MAY2001	
112	0717_00007	01OCT2001	
113	0720_00008	08MAY2001	
114	0727_00011	20AUG2001	
115	0732_00005	16APR2001	
116	0741_00002	23MAY2001	
117	0757_00012	21FEB2001	
118	0757_00043	24MAY2001	
119	0759_00004	10MAY2001	
120	0762_00004	01JUL2001	
121	0763_00003	05JUN2001	
122	0770_00002	02JUL2001	
123	0141_00016	11APR2001	
124	0715_00001	22FEB2001	
125	0769_00006	22MAY2001	
126	0727_00006		31OCT2001
127	0766_00002		23APR2001

APPEARS THIS WAY
ON ORIGINAL

The summary of events on IFN+Ara-C (based on ITT) is as follows (explanation on Table 9-17 is underlined):

- 36 progressions to AP/BC (29 on first-line, 2 on first-line after loss of CHR, 3 on second-line and 2 on second-line after loss of CHR >>> therefore 4 AP/BC events were included in Table 9-17 as 'Loss CHR' as these were the patients' first event)
- 35 loss CHR (as described above, 2 lost CHR on first-line and 2 lost CHR on second-line before they progressed to AP/BC >>> now counted as AP/BC but included in Table 9-17 as 'Loss CHR')
- 6 loss MCyR (another 3 patients lost MCyR and progressed to AP/BC at the same time, therefore were counted as AP/BC already)
- 24 increase in WBC (4 patients had increase in WBC but only after 'Loss of CHR' already, another three patients were considered in this category as they had increasing WBC and discontinued with reason 'Unsatisfactory therapeutic effect' instead of cross-over' patients 0141_00016, 0715_00001 and 0769_00006)
- 2 patients died during treatment

Therefore in the table derived from eff 1st and eff 2nd datasets, 2 patients with loss of CHR need to be subtracted (those who lost CHR on second-line?), as well as 2 patients with loss of MCyR and one patient with 'Increase in WBC' (= - 4 who had 'Loss CHR' + 3 with REASON=4):

108 events - 2 loss CHR - 2 loss MCyR - 1 increase in WBC = 103 events

Or alternatively (to get Table 9-17), list 4 AP/BC less (and therefore add two of them as 'Loss CHR'), but correct (subtract) two loss MCyR and one increase in WBC

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Monday, November 04, 2002 10:54 AM
To: statena@cder.fda.gov
Subject: Loss CHR

Importance: High


103102_FDA_TTP QUERY (answer 0.

Hi Ann,

In response to your recent query please find our response in the document
attached. Please let me know if there are any further questions or comments.

(See attached file: 103102_FDA_TTP QUERY (answer 04NOV02).doc)

Best regards,

Bob.....

TTP QUERY

NOVARTIS LOSS CHR NOT FDA

Please explain why the following patients were considered to have lost CHR on the LCHRDT_N dates of assessment.

Explanation: all the following patients had **early forms (=metamyelocytes+myelocytes) >=5%**
(SAS variable in A_EFFVIS = EARLY which is the sum of lab parameters MYL and MMYL from lab dataset A_LABH, i.e. only the myelocytes are also added to the dataset A_EFFVIS as variable MYL)

PT ID#	LCHRDT_N
0046_00002	12/19/2001 >> early forms >=5% on 19DEC01 (confirmed with >=5% on 16JAN02)
0054_00009	01/29/2001 >> early forms >=5% on 29JAN02 (confirmed with >=5% on 26FEB02)
0141_00014	06/27/2001 >> early forms >=5% on 27JUN01 (confirmed by 1% promyelocytes 08AUG01)
0717_00008	9/19/2001 >> early forms >=5% on 19SEP01 (confirmed with >=5% on 14NOV01)
0757_00026	06/25/2001 >> early forms >=5% on 25JUN01 without confirmation but patient crossed over for 'Loss of CHR'
0778_00001	11/19/2001 >> early forms >=5% on 19NOV01 (confirmed with >=5% on 02JAN02)

FDA LOSS CHR NOT NOVARTIS

Please explain why the following patients were **not** considered to have lost their CHR's on the dates assessed.

Explanation: As stated in Table 6-2 of the study report, loss of CHR is defined only when any of the following criteria is fulfilled and confirmed by a second assessment >= 4 weeks later which also shows any of the following:

- WBC > 20 x 10^9/L
- Platelets ≥ 600 x 10^9/L
- Appearance of blasts or promyelocytes >0% in PB
- Appearance of myelocytes + metamyelocytes ≥ 5% in PB
- Splenomegaly ≥ 5cm

As **all of the following were not confirmed**, these assessment were not considered 'Loss of CHR' (except patient 0714_00004 who had loss of CHR already on 26DEC01 due to 8% myelocytes)

PT ID #	ASSDT_N	STDDAY	FIELD	VALUE
0043_00002	12/06/2000	99	PML	3.1
0048_00012	04/10/2001	79	WBC	22.92
0065_00026	06/25/2001	174	DPLCNT	743
0158_00002	12/04/2000	102	PML	4
0160_00001	11/28/2000	113	PML	1
0714_00004	01/18/2002	507	WBC	24.2 >> has LCHRDT_N=26DEC01
0719_00003	03/01/2001	157	DPLCT	894
0727_00002	05/25/2001	255	DPLCT	985
0735_00004	9/13/2001	249	MYL	6.3

Staten, Ann M

From: Staten, Ann M
Sent: Monday, November 04, 2002 9:29 AM
To: Robert Miranda (E-mail)
Subject: Gleevec - s-004- more clinical questions

Importance: High

Dear Bob

Attached are more questions for your team PLease let me know if you can open this one

AC 2nd.doc

FDA not SPONSOR AC 2nd

Please explain why the following patients were **not** considered to be in accelerated phase on the STDDAY specified.

PT ID	STDDAY	COLUMN	VALUE
0026_00001	219	BAS	24
0065_00011	205	BLASTS	15
0151_00007	210	BLASTS	18

SPONSOR NOT FDA AC 2nd

Please explain why the following patient was considered to be in accelerated phase on the day specified. Although the WBC had increased to 139, the blast count was only 6% and I could find no other criteria for Accelerated phase that were satisfied.

PT ID	ACCEL_N	STDDAY	COLUMN	VALUE
0738_00015	12/27/2001	402	BLAST	6

FDA not SPONSOR LOSS CHR 2nd

Please explain why the following patients were **not** considered to have lost CHR on the STDDAY specified.

PT ID	STDDAY	COLUMN	VALUE
0002_00002	519	PML	1
0026_00003	426	BLASTS	2
0065_00023	359	BLASTS	1
0148_00004	357	PML	0.9
0152_00008	425	BLASTS	4
0714_00004	507	WBC	62.8
0732_00004	309	BLASTS	18
0756_00007	208	BLASTS	7

Staten, Ann M

From: Staten, Ann M
Sent: Thursday, October 31, 2002 4:34 PM
To: Kevin Carl (E-mail)
Subject: FW: Gleevec Query (S-004 CML)

Dear Bob

Attached are questions from the Medical Reviewer regarding S-004 (CML) application

thanks.

Ann

will be working at home tomorrow if you have any questions (301) 874-0198

TTP QUERY.doc

TTP QUERY

NOVARTIS LOSS CHR NOT FDA

Please explain why the following patients were considered to have lost CHR on the LCHRDT_N dates of assessment.

PT ID#	LCHRDT_N
0046_00002	12/19/2001
0054_00009	01/29/2001
0141_00014	06/27/2001
0717_00008	9/19/2001
0757_00026	06/25/2001
0778_00001	11/19/2001

FDA LOSS CHR NOT NOVARTIS

Please explain why the following patients were **not** considered to have lost their CHR's on the dates assessed.

PT ID #	ASSDT_N	STDDAY	FIELD	VALUE
0043_00002	12/06/2000	99	PML	3.1
0048_00012	04/10/2001	79	WBC	22.92
0065_00026	06/25/2001	174	DPLCNT	743
0158_00002	12/04/2000	102	PML	4
0160_00001	11/28/2000	113	PML	1
0714_00004	01/18/2002	507	WBC	24.2
0719_00003	03/01/2001	157	DPLCT	894
0727_00002	05/25/2001	255	DPLCT	985
0735_00004	9/13/2001	249	MYL	6.3

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Wednesday, October 09, 2002 8:25 AM
To: STATENA@cder.fda.gov
Subject: Re: Gleevec NDA 21-335/004

Importance: High

106-FDA comments-review of cas...

Dear Ann,

Here is our response to the clinical comments from your 10/8/02 e-mail:

(See attached file: 106-FDA comments-review of cases (08OCT02)-REPLY.doc)

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

"Staten, Ann M" <STATENA@cder.fda.gov> on 10/08/2002 09:37:45 AM

To: "Robert Miranda (E-mail)" <robert.miranda@pharma.novartis.com>
cc:
Subject: Gleevec NDA 21-335/004

This part of the message was ENCRYPTED

This part of the message was SIGNED by Email=statena@cder.fda.gov, ou="This certificate represents a secure server, not an individual.", o=FDA/CDER, cn=FDA/CDER Secure Server (proxy), who is certified by Email=secure-server@CDER.FDA.GOV, ou="This certificate represents a secure server, not an individual.", o=FDA/CDER, cn=FDA/CDER Secure Server

Dear Bob,

We have the following request regarding S-004:

1. Please provide your rationale for the determination of whether thrombocytopenia was or was not therapy-related. Was all thrombocytopenia presumed to be therapy-related while patients were on study?
>
2. Please explain why the following patients were considered to have

progressed into accelerated phase:

0147_00002, 0770_00001 and 0065_00017.

3. Please explain why the following patients were not considered to have
progressed to accelerated phase?

>
> SID # STUDY DAY LAB VALUE RNDTRT
> 0151_00007 210 BLASTS 18 2
> 0714_00004 442 BMSUM 30 2
>
>
Thanks,
Ann

Physician
Clinical Indication Leader

Tel +41 61 324 3413
Fax +41 61 324 5532

NOVARTIS

Reply to FDA query dated 8 October 2002

Authors: Martee L. Hensley, Insa Gathmann

Date: 09 October 2002

1. Please provide your rationale for the determination of whether thrombocytopenia was or was not therapy-related. Was all thrombocytopenia presumed to be therapy-related while patients were on study?

Novartis reply:
All thrombocytopenia was presumed to be therapy-related for all patients on both arms of the study. The rationale for this decision was that it would not have been consistently possible to determine which times in which patients a low platelet count may have been due to drug effect or to CML. Since thrombocytopenia was considered treatment-related in both imatinib and interferon+AraC arms, we note that the frequency of grade 3 or 4 thrombocytopenia was 7.1% in the imatinib arm, v. 16.3% in the interferon +AraC arm.

2. Please explain why the following patients were considered to have progressed into accelerated phase:

   0147_00002, 0770_00001 and 0065_00017.

3. Please explain why the following patients were not considered to have progressed to accelerated phase?

SID #	STUDY DAY	LAB	VALUE		RNDTRT
0151_00007	210	BLASTS	18	2	
0714_00004	442	BMSUM	30	2	

Novartis reply: Please see the listings that follow for details of each of the 5 cases queried in questions 2 and 3.

Country/ Center	Subject	Age/Sex/ Race	First line- Second line /start date	Visit	Visit date	Study Day	Investigator Comments

GBR/147 0002 67/F/Cau I/06SEP2000 18 **22AUG2001** 351 PAGE 111: TWO CELLS LINES WERE PRESENT. ONE LINE CONTAINED ADDITIONAL COPIES OF CHROMOSOMES 6 AND 8, A RECIPROCAL REARRANGEMENT BETWEEN CHROMOSOMES 9 AND 22 RESULTING IN THE PHILADELPHIA CHROMOSOME, AND ON APPARENT PERICENTRIC INVERSION OF ONE COPY OF CHROMOSOME 16. THE OTHER CELL LINE WAS NORMAL. THE CLONAL EVOLUTION IN THIS SAMPLE ISCONSISTENT WITH A STATE OF TRANSFORMATION.

777 **17SEP2001** 377 BLAST TRANSFORMATION OF CML.

>>> this patient discontinued due to 'Unsatisfactory therapeutic effect' on 17SEP01 and died 07FEB02 because of CML

Reason patient considered to have had disease progression: The patient's blast count was 8% on 22 Aug2001, On 17 Sep 2001, the day of discontinuation for progression, we were not provided with full marrow counts, but were provided with investigator's bone marrow diagnosis of "blast transformation". The patient did not cross over.

USA/770 0001 24/F/Cau I/13DEC2000 777 31JUL2001 231 SEE SAE SECTION, HOSPITAL RECORDS PAGE 96 - OTHER = ATYPICAL LYMPH.
EXTRAMEDULLARY INVOLVEMENT: LYMPH NODES/OTHER HIGH LEFT NECK: BIDIMENSIONAL MEASUREMENT HEIGHT = N/A X 2.5 CM. MEDICAL NOTES SUBMITTED INDICATE BLASTIC TRANSFORMATION AND BIOPSY-PROVEN BLASTS PRESENT IN THE LEFT SUPRACLAVICULAR NODES.THE NOTES ALSO CONFIRM THAT NO EVIDENCE OF INFECTION OR SURGICAL COMPLICATIONS WERE NOTED.EMD AT STUDY COMPLETION VISIT INDICATES EMD INVOLVEMENT AND AN SAE WAS REPORTED AT THIS TIME REGARDING LEFT ANTERIOR CERVICAL CHAIN LYMPHADENOPATHY.

>>> this patient discontinued due to 'Unsatisfactory therapeutic effect' on 26JUL01 (new data = patient is still alive 25JUN02).

Reason patient considered to have had disease progression: Patient developed extramedullary disease in the lymph node which was biopsy-proven to be blasts. This met our pre-specified criteria for disease progression as outlined in Table 6.2, page 57, of the Clinical Study Report.