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

DEU/065 0017 22/M/Cau I/30OCT2000 777 27NOV2000 29 SEE SAE (CHLOROMA)
PLEASE SEE PAGE 5: THORACIAL VERTERBRAL BODIES 6-10 (LOCATION OF CHLOROMA). BMA NOT PERFORMED. P5 EXTRAMEDULLARY INVOLVEMENT ASSESSMENT WAS PERFORMED BY MRI. PLEASE ALSO LOOK AT CORRESPONDING SAE -REPORT.
999 27FEB2001 121 DATE OF PROGRESSION TO CHLOROMA: 23NOV2000

>>> this patient discontinued due to 'Unsatisfactory therapeutic effect' on 22NOV00 (new data = patient is still alive 28JUL02).
Reason patient considered to have had disease progression: Although PB blasts were stable, the patient developed a new chloroma, confirmed by MRI, thus meeting criteria for new extramedullary involvement, consistent with disease progression.

GBR/151 0007 44/M/Cau I/19JAN2001
S/08AUG2001 777 27AUG2001 20 THE END OF STUDY VISIT WAS PERFORMED ON THE 20AUG2001. AT VISIT 14.03, THE PATIENT WAS DISCOVERED TO BE IN ACCELERATED PHASE, BUT WAS ONLY GIVEN PERMISSION BY NOVARTIS TO ENTER THE EXTENSION PHASE ON 29AUG2001. COMMENCED 29/08/01

>>> this patient crossed-over on 08AUG01 and had 18% blasts on 13AUG01. Values decreased thereafter, but as extension was permitted on 29AUG01 the patient discontinued STI571 within the study by electing instead to continue STI571 as part of the extension study (new data = patient is still alive 14JUN02).
Reason patient considered not to have progressed: The blast count of 18% was seen only 6 day after crossing over to STI571. As per stated guidelines in Table 6.2, page 57 of Clinical Study Report, events that occurred within 4 weeks of change of therapy were not considered progression.

USA/714 0004 52/F/Cau I/11SEP2000
S/23MAY2001 777 29JAN2002 252 RECURRENCE OF GRADE 3-4 ALT ELEVATION DESPITE STI571 DOSE MODIFICATION. PATIENT PREFERRED TO BE FOLLOWED BY HER LOCAL MD, COMMUTING TO THE CITY IS BECOMING A BURDEN.
PT. PREFERRED NOT TO COME BACK TO THE STUDY CENTER FOR FF-UP, WILL BE FOLLOWED BY HER LOCAL MD. LAST BLOOD WORK ON JAN 29, 2002 DONE AT HER LOCAL MD'S OFFICE, WE'LL TAKE THIS AS THE OFF-STUDY DATE, ALT=BACK TO NORMAL; ELEVATED WBC AND ELEVATED LDH SECONDARY TO DISEASE.

>>> this patient had 30% promyelocytes on 14NOV01 but was assessed by investigator as having CHR. Alos CHR was seen thereafter before discontinuation due to AE at which date time to AP/BC was censored. Patient had increasing WBC and promyelocytes on 29JAN02 (6 weeks after stopping STI571) (new data = patient is still alive 13MAY02).

Reason patient considered not to have progressed: On the same date that the BM assessment was read as 30% promyelocytes, the investigator stated that the patient was in CHR. The patient remained on study at that time, and subsequent assessment confirmed continued CHR. The patient eventually discontinued study drug, but this was for the AE related to ALT elevation, not disease progression.

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Friday, September 06, 2002 9:34 AM
To: statena@cder.fda.gov
Subject: Re: IMPORTANT - FDA Request for Gleevec Datasets

Importance: High

Dear Ann,

Here is the response from our biostatistician regarding the information requested in your fax dated September 4, 2002:

1) Safety and efficacy analyses by gender, age and race:

- The percentages of AEs by gender, age and race are found in Post-text supplement 3 of the study report (Vol. 12, page 8-160), consisting of Post-text table 10.6-3 by age (Vol. 21, page 8-21), Post-text table 10.6-4 by sex (Vol. 21, page 8-143) and Post-text table 10.6-6 by race (Vol. 22, page 8.1).

- The efficacy analyses by subgroups are included in the ISE (and not in the main study report). In section 6.2. of the ISE (Vol. 41, page 8-47) the CHR and MCyR rates (on first-line treatment) are summarized by demographics (sex, age, race). In section 6.3. (Vol. 41, page 8-47) of the ISE these rates are then summarized by Sokal and Hasford score.

2) Datasets A_AEV01 and A_AEV02:

As per FDA guidelines, the SAS transport files are allowed to have a certain size only, therefore the whole AEV dataset had to be split into 2 smaller ones. You would need to combine them if the datatset should include all AEs (please consider that all AEs with LINEGRP=611 occurred during first-line treatment, and all AEs which were reported with a start date after cross-over had LINEGRP=612).

3) Datasets A_EFF1ST and A_EFF2ND:

There are a total of three efficacy datasets which have one observation by patient summarizing the efficacy results (response rates, time to event variables).

A_EFFSBJ includes efficacy results as per ITT principle - taking all data regardless of cross-over to calculate response, TTP etc.

A_EFF1ST includes efficacy results for first-line treatment - taking all data before cross-over, i.e. responses after cross-over are not counted

A_EFF2ND includes efficacy results for second-line treatment only - taking data after cross-over only (in all patients who did cross over)

Therefore, in order to calculate for example the MCyR rate on first-line treatment, you have to summarize the variable BKR. You would use the same variable, but the dataset A_EFFSBJ if you want to get the results for the

ITT principle.

Please let me know if you have any further questions,

Best regards
Bob

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Bob Miranda, Novartis	**From:** Ann Staten, Project Manager
Fax: 973-781-5217	**Fax:** 301-827-4590
Phone: 973-781-3758	**Phone:** 301-594-0490
Pages: 1	**Date:** September 4, 2002
Re: NDA 21-335/001 Gleevec/S-004	

■ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Bob,

We have the following additional information requests:

1 We see no indication that you performed the required gender, age and race analyses for either safety or efficacy. Please confirm whether these analyses have been submitted. If not, they should be submitted as soon as possible.

2. What is the relationship of Tables a-aev01 and a-aev02?

3. What is the relationship of Tables a_eff1st and a_eff2nd?

Sincerely,

Ann /S/

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Bob Miranda, Novartis	**From:**	Ann Staten, Project Manager
Fax:	973-781-5217	**Fax:**	301-827-4590
Phone:	973-781-3758	**Phone:**	301-594-0490
Pages:	1	**Date:**	August 19, 2002
Re:	NDA 21-335/001 Gleevec/S-004		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Bob,

The Clinical review of Gleevec first line CML will be conducted using Microsoft Access. In the submitted electronic database in SAS Transport, two Tables in the Derived Datasets do not convert from SAS Transport to Microsoft Access. These Tables are A_EFF1ST and A_EFF2ND.

Please submit these two Tables in SAS Transport files that are convertible to Microsoft Access.

Sincerely,

Ann /S/

Staten, Ann M

From: Staten, Ann M
Sent: Friday, August 16, 2002 3:11 PM
To: 'robert.miranda@pharma.novartis.com'
Subject: sNDA 21-335/003 and 004 -PK assay for Studies 103 and 106

Importance: High

Dear Bob,

We have the following request from the Clinical Pharmacology Reviewer:

Please submit the following information:

Study number, pt ID, date of sample analysis, analytical method used, analytical method validation

If this data is available in the electronic data sets, could you let me know where to find them ?

Please let me know if there are any questions

Thanks,
Ann

MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS

DATE: November 7, 2002 (11:00am-11:30am)

SUBJECT: NDA 21-335/S-004 Gleevec (imatinib mesylate)

Discussion:

Ms. Paige Brown, patient advisory consultant, was consulted regarding the supplemental application for Gleevec in first line CML (study 106). Ms. Brown concurred with the Division's decision to approve this application.

/S/

Ann Staten, RD
Regulatory Health Project Manager

/S/

Peter Bross, MD
Medical Reviewer

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
12/4/02 09:51:43 AM
CSO

Peter Bross
12/4/02 11:10:02 AM
MEDICAL OFFICER

MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS

DATE: November 7, 2002 (1pm-1:30pm)

SUBJECT: NDA 21-335/S-003, S-004 Gleevec (imatinib mesylate)

Discussion:

Dr. Przepiorka was consulted regarding the supplemental application for Gleevec in first line CML (study 106). Dr. Przepiorka concurred with the Division's decision to approve this application. Because of the relatively short follow-up and few progressions especially with respect to accelerated phase and blast crisis, Dr Przepiorka suggested consideration of accelerated approval rather than full approval with the accelerated approval phase 4 commitment to include submission of more mature data (i.e., follow-up 5 years for complete survival and TTP to AP or BC). Dr. Przepiorka also would like to see the Statistical Reviewer's comments regarding time to progression to AP or BC (see question #4 of the attachment).

Dr. Przepiorka suggested that QoL data from this open label trial could possibly be useful depending on the outcome of the review.

Dr. Przepiorka was also consulted regarding pediatric CML. Since the disease is similar to adult CML, the adult data can be used to support an indication in children.

/S/

Ann Staten, RD
Regulatory Health Project Manager

/S/

Peter Bross, MD
Medical Reviewer

Attachment: FDA review questions

sNDA 21-335/ S-004
Drug: Gleevec™ (imatinib mesylate)
Sponsor: Novartis

Proposed indication: Gleevec™ (imatinib mesylate) is indicated for the treatment of patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (CML).

Study protocol for registration: Study No: CSTI571 0106

Title: A phase 3 study of STI571 versus Interferon a (IFN) combined with Cytarabine (Ara-C) in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP).

Study Design: This was a randomized, open-label, multicenter phase III study.

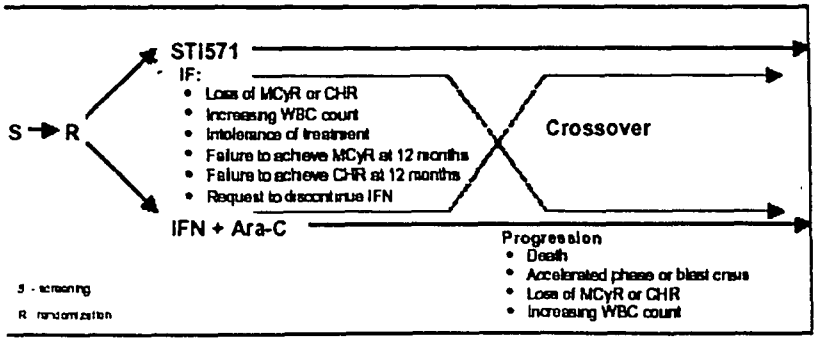
A copy of the sponsor's synopsis of their study report on their registration study 106 has been provided, which includes a table of study efficacy endpoints. The primary objective was to demonstrate the superiority of STI571 over IFN + Ara-C in terms of time to progression. The definition of progression included:

- Progression to accelerated phase or blast crisis
- Increasing WBC count defined as a doubling of > 20.0 x 10'/L
- Loss of CHR (at any time)
- Loss of MCR (at any time)
- Death due to any cause

Question 1: Do you agree that a significant prolongation in time progression of Gleevec compared to Interferon/Ara-C would constitute sufficient evidence of clinical benefit for conversion to full approval?

Crossovers were allowed, and criteria for crossover are illustrated in Figure 1. Crossover requests for intolerance or increasing WBC had to be approved by the study monitoring committee (SMT).

Figure 1: Study 106 crossover outline



Almost 40% of the patients who began on the Interferon/Ara-c arm crossed over to the Gleevec arm, whereas only 1% of patients originally on the Gleevec arm crossed over to the Interferon/Ara-c arm. All requests for crossover due to intolerance or increasing WBC had to be approved by the study management committee.

Table 1: reasons for Crossover

Progression :	3 (0.6)	49 (8.8)
Intolerance of treatment[1)]	4 (0.7)	126 (22.8)
No CHR at 6 months[2)]	0	41 (7.4)
No MCyR at 12 months[3)]	0	1 (0.2)
No MCyR at 24 months[3)]	0	1 (0.2)
Total Number of patients who crossed over	7 (1.3)	218 (39.4)

Question 2: Do the excessive numbers of patients who crossed over from interferon to Gleevec compromise the interpretation of the primary efficacy analysis?

The definition of accelerated phase and blast crisis included

- Accelerated phase is defined as the appearance of one of the following: blasts in the blood or bone marrow $\geq$ 15%, or percentage of blasts plus promyelocytes in the peripheral blood or bone marrow $\geq$ 30%, or peripheral basophils $\geq$ 20%, or thrombocytopenia $\leq$ 100 x 10'/L unrelated to therapy.

- Blastic phase is defined as blasts in the blood or bone marrow $\geq$ 30% or appearance of extramedullary involvement (e.g. chloromas), except for liver and spleen.

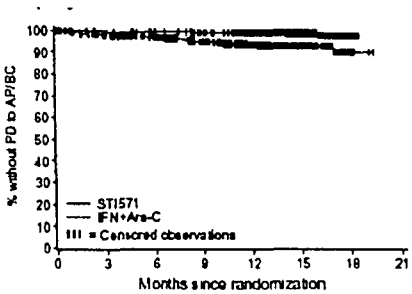
Question 3: The sponsor's analysis of time to accelerated phase or blast crisis excluded thrombocytopenia. All thrombocytopenia was presumed to be therapy-related for all patients on both arms of the study. The rationale for this decision was that it would not have been consistently possible to determine if a low platelet count was due to drug effect or to CML. Do you agree?

The sponsor's and FDA progression to accelerated phase events are summarized below.

Table 2 Progression to accelerated phase

Progression to accelerated phase		**Gleevec N (%)**	**IFN+Ara-C N (%)**
Sponsor	**First line**	**8 (1.4)**	**29 (5.2)**
	ITT	**10(1.4)**	**36 (5.8)**
	Log-rank test	**p<0.001**	
FDA	**First Line**	**8 (1.4)**	**31 (6.0)**
	ITT	**10 (1.8)**	**40 (7.2)**
	Log-rank test	**p<0.001**	

Figure 2: Time to progression to AP or BC (ITT principle)



Differences between FDA and sponsor were relatively minor and favored the sponsor.

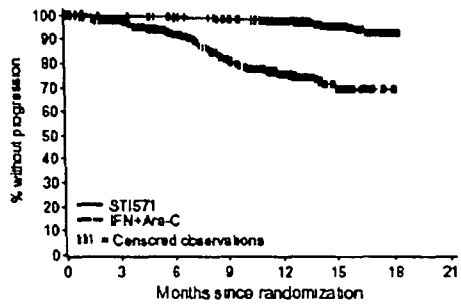
Question 4: Would a significant prolongation in time to accelerated phase and blast crisis constitute sufficient evidence of clinical benefit for conversion to full approval? Do the results of the preliminary analysis of time to accelerated phase and blast crisis summarized above represent sufficient clinical benefit for conversion to full approval?

The primary endpoint for full approval is the demonstration of superiority of Gleevec compared with interferon and ara-c in an intent to treat (ITT) analysis of time to progression (TTP). The planned cutoff date for the TTP analysis was the date of the 385th event. On the basis of a planned interim analysis of cytogenetic responses at 6 months, the study was closed early after a minimum of 12 months follow-up. At the time of analysis, there were 24 and 103 events of progression respectively for the Gleevec and IFN+Ara-C arms. Sponsor's and FDA preliminary results of progression events are summarized below.

Table 3: Sponsor's vs FDA TTP events (ITT principle)

	STI571 N=553 (%)	**IFN+Ara-C** N=553 (%)
Sponsor's Results of analysis of TTP events		
Death (as primary reason for discontinuation)	4 (0.7)	2 (0.4)
Progression to AP or BC	**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)
Total no. of patients with events (progression)	**24 (4.3)**	**103 (18.6)**
Log-rank test / Wilcoxon test	**p<0.001**	
Preliminary FDA Results of analysis of TTP events		
Death (as primary reason for discontinuation)	4 (0.7)	2 (0.4)
Progression to AP or BC	**8 (1.4)**	**33 (6.5)**
Loss of CHR	**12 (2.1)**	**36 (6.3)***
Loss of MCyR	7 (1.2)	8 (1.4)
Increase in WBC ≥ 20 on ≥ 2 visits	3 (0.5)	36 (6.5)
Total no. of patients with events (progression)	**34 (6.1)**	**115 (20.7)**
Log-rank test / Wilcoxon test	**p<0.001**	

Figure 3: Sponsor's Time to Progression (first line treatment)



The FDA analysis of TTP is preliminary. Minor differences between the FDA and sponsors results are currently being evaluated. The rate of loss of CHR was a complex endpoint, requiring 2 visits to confirm CHR followed by 2 visits to confirm progression on maximum tolerated therapy. Increase in WBC as evidence of progression was required to be approved by the study monitoring committee prior to crossover, however the FDA reviewer performed an exploratory analysis based on increase in WBC regardless of the SMC approval status.

At the time of the sponsor's interim analysis, assuming either 125 or 149 events of progression, the TTP results are quite highly statistically significant favoring the Gleevec arm. The FDA statistical reviewer estimated that, assuming if for the 258 remaining events needed to achieve the study goal of 385 events, the hazard ratio were to be 1, the chance of rejecting the null hypothesis that the two theoretical distributions for TTP are the same (and favoring Gleevec) is roughly 96.9%. It is therefore highly likely that the results of the final analysis will continue to show a statistically significant decreased risk of progression for patients treated with Gleevec compared with Interferon/Ara-c.

Question 5: Do you agree that the results summarized above, based on the interim analysis which demonstrated a significant prolongation in time progression of CML in patients treated with Gleevec compared to Interferon/Ara-c, constitute sufficient evidence of clinical benefit for conversion to full approval?

Labeling issues

Question 6: Should quality of life data analyses be allowed in the label based on results of this open-label trial showing that "patients maintain their well-being while on treatment with Gleevec?"

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
12/4/02 09:39:48 AM
CSO

Peter Bross
12/4/02 09:48:38 AM
MEDICAL OFFICER

MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS

DATE: November 19, 2002 (10am-11am)

SUBJECT: NDA 21-335, S-004 Gleevec (imatinib mesylate)

Discussion:

The Division called Novartis to inform Novartis that the Division was planning on an accelerated approval (subpart H) for the first-line CML supplement (S-004) due to the limited data on duration. The accelerated approval phase 4 post-marketing commitment would include submitting to the NDA follow-up on study 106 on an annual basis.

Novartis shared that the final reports for studies 102, 109 and 110 would be submitted late December or early January but that the results did not have any negative findings and that progression rates were extremely low.

The FDA clinical pharmacology reviewer shared the concern that and the recommended adult dose of 400mg did not have the same AUCs. Further discussion would take place via written correspondence.

Ann Staten, RD
Regulatory Health Project Manager

Peter Bross, MD/ Alla Shapiro, MD
Medical Reviewers

MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS

DATE: November 7, 2002 (8:30am-9:00am)

SUBJECT: NDA 21-335/S-004 Gleevec (imatinib mesylate)

Discussion:

Dr. Cheson was consulted regarding the supplemental application for Gleevec in first line CML (study 106). Dr. Cheson concurred with the Division's decision to approve this application with the phase 4 commitment to include submission of more mature data every 6 months for the first year and then annually.

/S/

Ann Staten, RD
Regulatory Health Project Manager

/S/

Peter Bross, MD
Medical Reviewer

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
12/4/02 09:52:56 AM
CSO

Peter Bross
12/4/02 11:13:58 AM
MEDICAL OFFICER

INTERNAL MEETING MINUTES

MEETING DATE: March 26, 2002

IND/NDA IND [redacted] Meeting Request Submission Date: January 31, 2002 (N454)
Briefing Document Submission Date: March 4, 2002 (N476)

DRUG: Gleevec (imatinib mesylate)

SPONSOR/APPLICANT: Novartis

TYPE of MEETING:

1. pre-sNDA

FDA PARTICIPANTS:
Richard Pazdur, M.D., Director, Division of Oncology Drug Products (DODP)
Grant Williams, MD, Deputy Director, DODP
Gani Chico, MD, Medical Team Leader
Martin Cohen, M.D., Medical Reviewer
John Leighton, PhD, Pharmacology/Toxicology Team Leader
Kimberly Benson, PhD, Pharmacology/Toxicology Reviewer
Mark Rothmann, PhD, Statistical Reviewer
Yung-Ao Hsieh, PhD, Chemistry Reviewer
Lilia Talarico, MD, Associate Director, DODP
Ann Staten, RD, Project Manager
Bruce Cheson, MD, ODAC
Paige Brown, Patient consultant

MEETING OBJECTIVES:

1. To discuss the sNDA submission of Gleevec for first-line CML (study P106).

BACKGROUND: Following the internal pre-meeting on 3-26-02, FDA's responses were sent to the sponsor in a facsimile dated 3-27-02 (attached). The sponsor requested that the meeting be cancelled since clarification was not needed.

ACTION ITEMS:

There were no unresolved issues or discussion points.

/S/ /

Ann Staten Date
Project Manager
Minutes preparer

Concurrence Chair: /S/ /

Martin Cohen, M.D. Date
Medical Reviewer

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building

To: Bob Miranda	**From:** Ann Staten, Project Manager
Fax: 973-781-6325	**Fax:** 301-827-4590
Phone: 973-781-2282	**Phone:** 301-594-5770
Pages: 8	**Date: March 27, 2002**

Re: IND [redacted] Gleevec - pre-sNDA meeting; breifing package dated March 4 and 14, 2002

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Bob,

Attached are the FDA answers to your questions. You have the option of canceling our meeting of March 29, 2002 if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible if you are canceling the meeting.

Regards,

ann

FDA Pre-SNDA Meeting – March 29, 2002
Questions

Chemistry, Manufacturing and Controls

1. The treatment of newly diagnosed CML in adults — will use the same drug product as currently approved in our NDA, therefore no CMC section is planned for this SNDA. Do you agree with this approach?

FDA Response:
We wish to remind you that all applications (e.g., sNDAs) requesting agency action require the submission of an EA or a claim of categorical exclusion. Under the revised 21 CFR Part 10, your sNDA qualifies for a categorical exclusion, if action on this submission does not increase the use of active moiety, or results in increased use of the active moiety, but the expected introduction concentration (EIC) at the point of entry into the aquatic environment will be below 1 ppb.

It is recommended that you review your data and determine whether an EA or a claim of categorical exclusion should be submitted. Please note that the standard EIC calculation is included in the EA Industry Guidance and the calculation should be based on the kg of the active moiety used in the entire product line for Gleevec.

Preclinical

2. Our original NDA for CML contains all existing relevant preclinical safety data for Gleevec. Since the filing of this original NDA, one additional preclinical safety study is ongoing. The final report for this study will be included in the planned SNDA. This will complete the reproductive toxicity studies with the compound. An outline of this study is given in section 4.1 and is identified as Study no. 017021: STI571: An oral pre- and postnatal development study in rats".

Additional reports which have been issued in the Preclinical Drug Metabolism and Pharmacokinetics Department since the original NDA are listed in Attachment 10, and are not planned to be included into the SNDA for the newly diagnosed CML — They are available on request and will be included in the next IND annual report.

Do you agree with this approach?

FDA Response:

We request that you also submit study number R00-097-01, "Metabolism in milk and plasma after a single peroral administration of [c-14]STI571 to lactating rats", with the SNDA.

3. Proposed carcinogenicity study protocols, taking into account the ICH Harmonized Tripartite Guidelines S1C "Dose Selection For Carcinogenicity Studies of Pharmaceuticals" and S1B "Testing for Carcinogenicity of Pharmaceuticals" have been submitted to FDA on February 15, 2002 (Serial Nos. 467 & 468) and are pending comments and approval. Assuming a timely review and agreement

on these studies, it is foreseen that the 2-year rat carcinogenicity study will be on-going at the time of submission (June 2002), and that the 26-week study inTgHras2 transgenic mice will be initiated in 3Q02.

We believe that the timing of these carcinogenicity studies is supported by the ICH Harmonized Tripartite Guidelines S1A "Guideline on the need for carcinogenicity studies of pharmaceuticals", and justified because of the overwhelming superior efficacy of Gleevec in study B106 with regards to all efficacy endpoints and the clearly favorable safety profile in comparison with IFN and cytarabine, thus providing a significant improvement over existing therapies for patients with this serious and life-threatening disease.

Do you agree with this approach?

FDA Response:

Your time frame for submission of carcinogenicity studies is acceptable.

Clinical Pharmacology

4. An overview of the clinical pharmacology program for this SNDA is provided in section 4.2 of the briefing documentation and consists of data on population PK from STUDY 0106, pediatric PK from P0103 and drug-drug interaction with rifampicin. We believe the studies conducted are adequate to support labeling for the treatment of newly diagnosed Philadelphia positive CML patients. Do you agree?

FDA Response: Yes

Clinical and Statistical

(Filing for newly diagnosed treatment of CML)

5. Novartis is intending to file the present application to add labeling for the treatment of newly diagnosed Philadelphia positive CML. This filing will be based on the results of study 0106 after a minimum of 12 months of follow-up, with the assumption that the 12 months data will confirm the presently available 6 months data in showing a consistently significant superiority of the Gleevec™ arm vs. the IFN+Ara-C arm for all efficacy endpoints (hematologic response, cytogenetic response, time to progression, time to accelerated phase or blast crisis). Does the FDA concur with the proposed filing strategy?

FDA Response:

The data presented on cross-over and discontinuation of treatment (Section 3.3.6.2) are compelling, but seems premature for an NDA submission when compared to the prospectively specified number of events required by the protocol. Please explain why you intend to submit the application early. How will the robustness of the results of progression free survival be assured?

(Data presentation for study 0106

6. Novartis has outlined in Attachment 8 our intended presentation of efficacy and safety data for the key efficacy trial 0106. This attachment provides details on the definition of patients populations, treatment variables (first line treatment, second line treatment, crossovers), efficacy variables and endpoints, safety analyses, and statistical analysis methods.

   Does the FDA concur with the proposals for the efficacy and safety analyses as summarized below:

   - Definition and use of patient populations for analyses of safety and efficacy (ITT, safety, per-protocol populations)

   FDA Response:Yes

   - Presentation of data by treatment period (ITT approach, first line treatment, second line treatment)

   FDA Response: Yes

   - Structure of safety tables and listings

   FDA Response: Yes

   - Efficacy analyses: definition of endpoints (CHR, MCR at 12 months, time to progression, time to accelerated phase or blast crisis, overall survival), definitions and timing of events/censored observations

   FDA Response:

   Failure to achieve a CHR at 6 months or MCyR at 12 months is not an efficacy endpoint

   Regarding cytogenetic response unconfirmed responses should not be counted. If an individual has a CCyR on one occasion and a PCyR on a second evaluation it will be scored as a PCyR. If the order is reversed and no subsequent study is done it is still a PCyR.

7. [redacted]

   FDA Response: Yes.

(Integrated efficacy summary)

8. This SNDA is based primarily on a single pivotal large phase III study for the front line CML indication — The objectives and the patient populations of these trials are very different. As a result, pooling of key efficacy data from these studies would not be meaningful.

   Therefore, we propose to present in the ISE (NDA Section 8) a discussion of the key results of the individual two studies in two separate sections as outlined in section 4.4. Do you concur with this approach to the presentation of efficacy data across the studies?

   FDA Response: Yes

(Integrated Safety Summary)

9. The present SNDA is essentially based on a single pivotal phase III randomized study in which 553 patients were randomized to Gleevec™ and 553 to a combination of IFN and cytarabine, — — an update of the GIST pivotal study. Under these circumstances, pooling of the data from these trials will not be meaningful.

   Do you concur with the proposed structure of the ISS as outlined in section 4.5, with a side-by-side presentation of the safety data from the phase III study 0106, — SAE from the phase II trials and an update of the GIST phase II study 2222?

   FDA Response: Yes

10. The composition of Section 10 (statistical section) of the NDA is largely a duplication of information contained in Section 8 (clinical section) of the NDA. We propose to submit in Section 10 identical copies of the relevant NDA volumes from Section 8, however, they would be provided in the color-coded covers for the statistical section. These volumes would bear the same volume and page numbers as well as the original section numbering from Section 8. Is this proposal acceptable?

    FDA Response: Yes

(Case Report Tabulations)

11 Do you concur with the extent of CRTs as described in Section 4.6. of this document to satisfy the requirements of 21 CFR 314.50(f)(1)?

   FDA Response: Yes. However, it is noted that there is a discrepancy between section 4.6 and 4.8 regarding the pharmacokinetic data to be submitted. Please change the contents of section 4.8 accordingly.

(Narratives and Case Report Forms)

12. Is the proposal for submission of narratives and CRFs described in Section 4.7. of this document acceptable?

    FDA Response: Yes

Electronic Submission

13. Does the FDA concur with our proposed electronic submission of documentation as outlined in section 4 of this document?

    FDA Response: Yes

14 In the Guidance issued in January 1999 it is suggested that font sizes smaller than 12 points should be avoided whenever possible. Significant programming has already been done for our data displays based upon 9 point (Courier new) font size. Will it be acceptable to submit these data displays using 9 point fonts?

    FDA Response: Yes

Regulatory Considerations

(Financial Disclosure)

15. We propose to submit the appropriate Financial Disclosure certification in accordance with the Final Rule published in the December 31, 1998 Federal Register for all investigators who enrolled patients in Studies 0106. These studies are the basis for establishing the safety and efficacy of Gleevec for the proposed indication. Is this acceptable?

    FDA Response: Yes

(Priority Review)

16. We intend to request a priority review at the submission of this SNDA. We believe that Gleevec provides a significant improvement over existing therapies for new diagnosed patients with Philadelphia positive CML. Would the consistent superiority of the Gleevec arm with regards to all efficacy endpoints and the clearly favorable safety profile in comparison with IFN and Ara-C support a priority review?

    FDA Response: This is a review issue to be answered after submission.

(Draft SNDA Table of Contents)

17. Provided as Attachment 9 is a draft table of contents for this SNDA which was designed to provide organization and outline all of the data included in this SNDA. Is this acceptable?

    FDA Response: Yes

Additional Chemistry question:

18. [redacted]

FDA Response:

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ON ORIGINAL

OTHER FDA COMMENTS:

1. NDA/sNDA Presentations to CDER's Division of Oncology

The Center for Drug Evaluation and Research's Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

3. Pediatric Final Rule

Please note that you will need to have addressed the December 2, 1998 Pediatric Rule (63 FR 66632) when you submit your NDA unless your product/indication has been designated an Orphan Drug. You may be eligible for a waiver under 21 CFR 314.55(c). Please refer to http://www.fda.gov/ohrms/dockets/98fr/120298c.txt. You may also refer to the draft guidance at http://www.fda.gov/cder/guidance/3578dft.htm.

4. [redacted]

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
4/17/02 11:38:09 AM

Martin Cohen
4/17/02 12:53:44 PM

2. **Regarding subsequent registration in newly diagnosed chronic phase CML**

   a. Does the randomized, controlled trial (Protocol 0106) described in section 4.1 support an initial registration in newly diagnosed chronic phase CML based on an analysis of the 6-month complete hematologic response rate and quality of life?

FDA Response:

No.

The 6-month complete hematologic response rate has not been demonstrated to be an adequate surrogate for survival or other clinical benefit. See references 11 (Ohnishi), 13 (Hehlman-German Study), 14 (Ozer), 18 (Kluin-Nelemans-Benlux Study) of briefing package and Silver RT et al. Blood 1999;94:1517-36.

Six RCTs of Interferon for initial treatment of CML have been published between 1994 and 1998. In only one of these RCTs were patients crossed over to the other treatment or removed from study based on failure to have a CHR by 6 months or failure to have a MCR by 2 years.

In the Ohnishi RCT use of CHR as a surrogate would have resulted in accelerated approval of Busulfan when survival turned out to be better on the Interferon treatment arm. In the German RCT use of CHR as a surrogate would have resulted in accelerated approval of Hydrea when median survival was 10 months longer on the Interferon treatment arm. In the Benelux RCT CHR was much better on the low dose Interferon treatment arm, but survival was identical on both treatment arms. Thus, use of CHR as a surrogate for survival would have resulted in the wrong conclusion in three of the four Interferon RCTs for initial treatment of CML for which information on CHR is available.

In the German Study, the Ozer Study and the Mahon Study about 50% of the patients with CHR first developed the CHR after 6 months.

The follow-up interval is too short to reliably estimate quality of life improvement.

It is highly unlikely that accelerated approval for newly diagnosed CML could be given based solely on better QOL (i.e., fewer side effects than interferon does not document efficacy) as measured by the proposed FACT-BRM quality of life instrument. There would need to be a demonstration of a strongly favorable effect on other QOL measures such as disease related symptoms.

Demonstration of superiority with major cytogenetic response (MCR), as a primary endpoint, at 24 months may be acceptable for Accelerated approval. The primary analysis will be intention-to-treat, i.e., patients with a MCR who were randomized to interferon and crossed over to STI571 before 24 months will be counted as a responses on the interferon arm. Extensive crossover will reduce the ability of the trial to detect differences in MCR (see also answer to 2.b.).

Question 2:

b. Does the planned analysis of time to treatment failure at 5 years in the newly diagnosed chronic phase CML trial provide adequate confirmation of the safety and efficacy of STI571 relative to interferon? Would this support full approval for all indications registered under Subpart H provisions?

FDA Response:

No.

The proposed definition of TTF is unacceptable as a primary efficacy endpoint.

Failure to achieve CHR at 6 months is not an adequate surrogate for survival or other clinical benefit.

We suggest the primary efficacy endpoints of study 0106 to be used as the basis of full marketing approval should be

1. **Time to onset of accelerated phase or blast crisis or**
2. **Time to Death**

Regarding the criteria for crossover in study 0106, the present criteria would result in crossover too early for too many patients, impairing the capacity to assess the effect of treatment on overall survival and time to blast crisis or accelerated phase.

Redacted 1

pages of trade secret and/or confidential commercial information

Additional FDA Comments:

A. Statistical

1. **For protocol 106**

   The log-rank test should be the primary analysis for time to event endpoints. Cox regression analyses should be considered as secondary analyses.

2. **For protocol 109**

   You did not respond to the first statistical comment (dated 8-27-99) for protocol 109. In that submitted protocol you stated the following, *"Depending on efficacy results and rate of enrolment, the total number of patients recruited per disease group may be expanded."* You should clarify how you intend to use efficacy results and rate of enrolment to expand the total number of patients per disease group.

B. Clinical Pharmacology & Biopharmaceutics

1. **Briefing Package (s/n 035):**

   a. We strongly recommend that you attempt to make PK correlations with adverse effects experienced with STI 571.

   b. **Study 102** – Please provide your detailed pharmacokinetic plan for the protocol.

   c. **Study 106 and 109** – Please provide a detailed description of your population pharmacokinetic analysis in these two protocols.

   d. Additional comments on addendum dated March 2, 2000 for study 106 to follow.

   e. **Study 110** – You stated that "considerable intrapatient variability exists for pharmacokinetic parameters that may be related to efficacy such as Cmax and AUC". Please

clarify (could it be due to change in tumor burden load; or patients with tumor lysis syndrome that may go into ARF and protein binding properties of the drug being displaced; look at responders vs non-responders to see if variability decreases).

f. You stated that intrapatient dose escalation may occur to 400 mg twice daily dosing. The pharmacokinetic parameters for these patients should be evaluated separately from patients that are not dose escalated to twice daily dosing.

g. In this setting, patients can serve as their own controls if pharmacokinetic sampling has taken place.

2. **Briefing package addendum (s/n 040):**

a. Please provide a detailed protocol/analysis plan of the population pharmacokinetics portion of the study.

You did not provide information as to which pharmacokinetic parameters will be calculated and what pharmacodynamic correlations will be attempted.

b. Please provide the study results from your food effect study as soon as they become available.

C. Regulatory

1. **Final Protocols**

Please submit final protocol(s) to the IND for FDA review, including a reference to this EOP2 meeting and a request for FDA feedback. We recommend you use a bolded identifier at the top of your cover letter – **"RESPONSE TO EOP2 MEETING"** and provide a desk copy of this cover letter to the project manager.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective, or that makes a significant contribution to demonstration of safety.

Please refer to the "Financial Disclosure by Clinical Investigators Final Rule Summary" (copy provided to Novartis).

3. Pediatric Final Rule

On December 2, 1998, the FDA published a final rule requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients (63 FR 66632). This became effective on April 1, 1999. Under this regulation, any application approved after April 1, 1999 must contain the appropriate pediatric studies or contain a waiver or deferral for pediatric studies (21 CFR 314.55 or 601.27).

You may be eligible for a deferral of pediatric studies under 21 CFR 314.55(b), or a partial waiver under 21 CFR 314.55(c)(3) for younger pediatric age groups. Please submit either:

(a) a pediatric drug development plan, or
(b) a request for deferral, or
(c) a request for waiver of required pediatric studies.

4. Pediatric Exclusivity

Under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension if STI 571 is appropriate for an indication in pediatrics. If you choose to pursue pediatric exclusivity, your plans for a pediatric drug development, in the form of a Proposed Pediatric Study Requirement (PPSR), should be submitted so that we can consider issuing a Written Request.

Please refer to the "Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act".

APPEARS THIS WAY
ON ORIGINAL

UNRESOLVED ISSUES REQUIRING FURTHER DISCUSSION:

1.

2.

3.

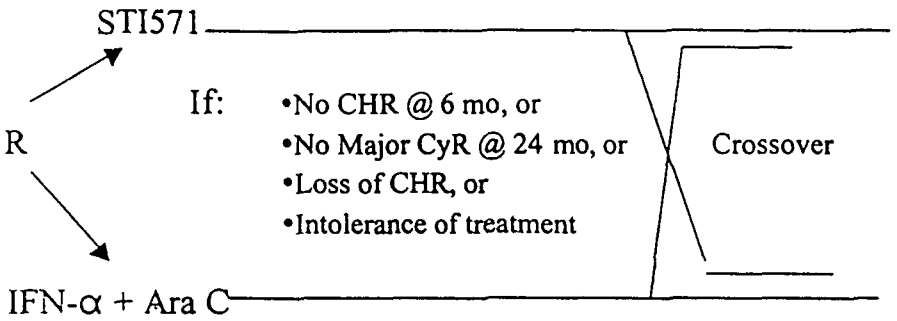
4.

ACTION ITEMS:

Item	Responsible Person	Due Date	Completion Date
1. Provide copy of FDA minutes to Novartis.	D.Spillman, FDA	NLT 6-2-00	_____
2.			_____
3.			_____
4.			_____
5.			_____

The meeting concluded at approximately ____ p.m.

Schema



Treatment Failure

- Crossover
- Progression to AP or BC before Crossover
- Death

Comparison of IFN-α ± Hydroxyurea + Ara C Regimens

NEJM Regimen vs STI 571 Regimen

NEJM

Hydroxyurea (50 mg/kg/d adjusted for WBC count) and IFN-α were given simultaneously until CHR.

IFN-α 5 million units/d s.c. from day 1 of treatment

Ara-C 20-40 mg/m2/d x 10-15 days q month s.c. beginning on day 14 of the cycle until confirmed CCyR.

STI571

Concurrent administration of Hydroxyurea is permitted only during the first 3 months of study treatment to keep the WBC count $<20 \times 10^9/L$

Ara-C 20 mg/m2/d x 10 days q month beginning on day 14 of the cycle until confirmed CCyR. Ara-C dosing starts after IFN-α dose reaches 5 million units/d

IFN-α dose may be gradually increased over 4 weeks to 5 million units/d s.c.

STI571 - Protocol 0106

Choice Of Interferon + Hydroxyurea As Comparator Regimen

Basis: French CML Study Group NEJM 1997;337:223-9

Statistical Analysis

To minimize the sample size and obtain results more rapidly, the study was conducted as a sequential trial using the triangular test.

The accumulated data were examined after approximately every 15 deaths.

At each sequential analysis, the z and V statistics were calculated. A positive z value indicated that interferon plus cytarabine was superior to interferon alone, and a negative value indicated that interferon plus cytarabine was inferior. The V statistic is related to the number of deaths. Once the sequential values of z and V were calculated, they were plotted, and the sample path was compared with the stopping boundaries. If the plotted point lay above the upper boundary (indicating that interferon plus cytarabine was more effective than interferon alone) or below the lower boundary, the trial had to be stopped.

721 patients were entered and there were 115 deaths

STI571 - Protocol 0106

Choice Of Interferon + Hydroxyurea As Comparator Regimen

Major Side Effects That Led to The Discontinuation Of Treatment , According To Treatment Assignment

SIDE EFFECT	INTERFERON CYTARABINE (N = 360)*	INTERFERON (N=361)†
Hematologic toxicity		
Thrombocytopenia	20	8
Other	31	9
Gastrointestinal		
Nausea, vomiting, diarrhea	45	14
Mucositis	21	2
Other	1	1
Weight loss, asthenia	48	20
Skin rash	19	7
Fever, flu-like syndrome, or both	10	7
Neurologic symptoms		
Peripheral	2	4
Central	7	4
Psychiatric disorder		
Depression	15	21
Other	13	19
Cytolytic hepatitis	9	3
Other side effects	31	32
Total no. of patients‡	179	113

* Eighty-five patients in this group discontinued cytarabine treatment. 45 discontinued interferon, and 49 discontinued both treatments.

† Sixteen patients in this group who did not have complete hematologic remission after six months subsequently received cytarabine and then discontinued that treatment, 81 discontinued interferon, and 16 (who also crossed over to receive interferon and cytarabine after six months) discontinued both treatments.

‡ The total number of side effects exceeds the total number of patients who discontinued treatment, because some patients discontinued treatment because of more than one side effect.

Time to CHR

Percent of Total CHR's Who Attain That Status After 6 Months of Interferon

Source	# of study patients	# of CHR's	% CHR @ 6 mo
Hehlmann	110	31	~45
Ozer	107	24	~60*
Mahon	116	93	~55

* Includes both CHR's and PHR's

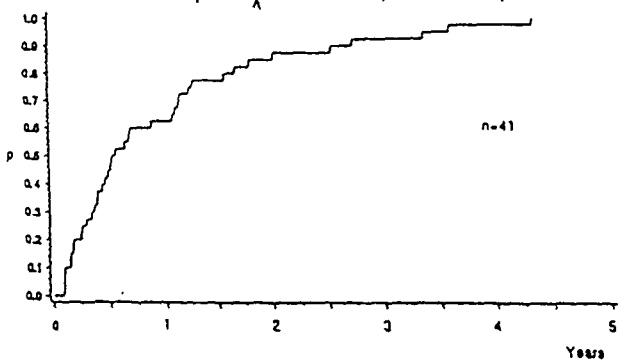
Time to MCyR

Percent Of Total MCyR's Who Attain That Status Within 24 Months After Starting Interferon

Source	# of study patients	# of MCyR's	% MCyR @ 24 mo
Tura	218	41	68
Ozer	107	31	~82
Mahon	116	50	~95
Allan	269	30	Median time to MCyR 84 w (16-164) & to CCyR 108 w (24-292)
MDACC	--	176	Median time to MCyR 12 mo (3-75) & to CCyR 16 mo (3-70)

HEMATOLOGIC

Time to Complete Remission, IFN Group



Hehlman R, et al Blood 1994;84:4064-77

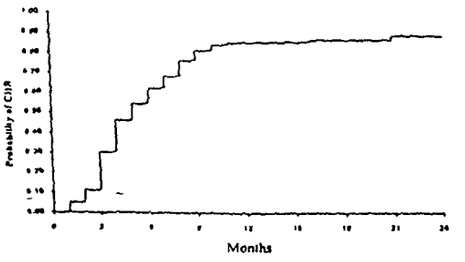


Fig 1. Cumulative incidence of complete hematological response (CHR) among the 116 patients.

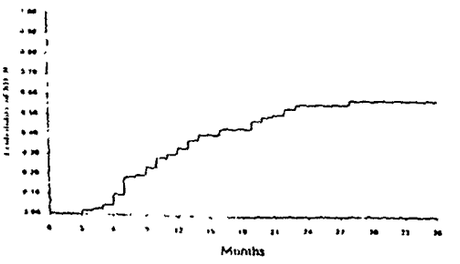
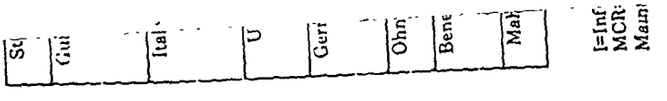


Fig 2. Cumulative incidence of MCR over time among the 113 evaluable patients.

Mahon FX, et al. Blood 1998;92:4059-65



Median Survival in CML After Development of Presumed Accelerated-Phase Characteristics

Characteristic	No. of Patients Developing Characteristics	Median Survival (mo)
Peripheral blasts ≥ 15%	85	8.6
Marrow blasts ≥ 15%	34	10.9
Peripheral blasts+ promyelocytes ≥ 30%	32	4.7
Marrow blasts+ promylocytes ≥ 30%	38	17.4
Peripheral basophils ≥ 20%	74	16.0
Marrow basophils ≥ 20%	25	11.6
Platelets <100,000/μL	105	14.9
Platelets >2 x 106 /μl_	76	27.2
Hemoglobin <7g/dL	92	16.0
Nucleated red cells ≥ 15%	60	23.5
Cytogenetic clonal evolution	54	7.0
Extramedullary disease	25	10.0

Significance Of Cytogenetic Clonal Evolution In Patients (Pts) With Ph+ CML

Prognostic Factors	No of Patients	Median Survival (mo)
No chromosome 17 abnormality + abnormal metaphases < 16% + interval to CE <25 months	37	54
Chromosome 17 abnormality and ≥34% abnormal metaphases	27	6
Other accelerated features and ≥16% abnormal metaphases	22	7
Other cytogenetic features	-	13-24

Multivariate analysis – poor prognosis variables

1. Chromosome 17 abnormality
2. Higher percent abnormal metaphases (cut off 25%)
3. Longer time to CE (cut off 25months)
4. No prior IFN-A therapy

Pts with none, 1, 2, 3 or 4 of these 4 features had median survivals of 51, 24, 14, and 7 months, respectively.

Definitions of IFN Resistance and Intolerance

Protocol STI571 0110 Ph+ CML in the chronic-phase of the disease, phase II

For crossover patients must have documented resistance or intolerance to an interferon-alpha containing therapy, defined as any of the following:

Resistance

a) Failure to achieve a complete hematologic response, lasting for at least 1 month despite 6 or more months of an interferon-alpha containing regimen. in which interferon was administered at a dose of at least 25 million international units (MIU) administered per week; during this treatment period the cumulative duration of hydroxyurea therapy may not exceed 50% of the treatment period with the interferon-alpha containing regimen.

b) bone marrow cytogenetics showing ≥65% Ph chromosome positivity after one year of interferon-alpha based therapy,

c) an increase in the Ph+ chromosome bone marrow cells by at least 30 percentage points (e.g., from 20% to 50%, or from 30% to 60%) confirmed by two samples at least 1 month apart, or an increase to ≥ 65%

Intolerance

a) ≥Grade 3 non-hematologic toxicity, persisting for more than 1 month, in a patient receiving an interferon-alpha containing regimen that has been administered at a dose of at least 25 MIU/week. Patients who are intolerant to interferon-alpha must be more than 6 months from time of diagnosis.

Protocol STI571 0106 Ph+ CML in the chronic-phase of the disease, phase III

Resistance

a) Failure to demonstrate a CHR at 6 months or.

b) Failure to achieve a MCyR at 24 months. or

c) Loss of complete hematologic response, provided that progression to accelerated or blastic phase did not occur.

Intolerance

a) grade 3 IFN-a-related non-hematologic toxicity, persisting for more than 1 month despite appropriate dose reductions and optimal medical management. with IFN-a administered at a dose of at least 25 MIU/week. A documented ≥ grade 3 IFN-a-related non-hematologic toxicity that is life-threatening such that re-treatment with IFN-a would be deemed medically inappropriate is also considered intolerance of treatment.

In order to monitor study conduct. a steering committee composed of members external to Novartis will evaluate safety and efficacy data including crossover events throughout the course of the trial. Additionally, approval by the steering committee will be required before crossover due to intolerance of treatment occurs.

Dose modifications

Non-hematological toxicities

IFN-a associated toxicities. e.g. fatigue, depression, neurotoxicity, etc:

- for grade 2 toxicity proceed to a 25% dose reduction of IFN-a
- for grade 3/4 toxicity interrupt IFN-a until recovery and resume at 50% of the IFN-a dose

Hematological toxicity

If a patient experiences a Grade 3/4 hematological toxicity while on treatment with IFN-a + Ara-C defined as an ANC < 1.0 x 10^9/L and/ or a platelet count < 50 x 10^9/L, Ara-C must be interrupted. Ara-C treatment may be resumed if at the time of the next cycle the ANC count >1 .5 x 10^9/L and platelet count > 100 x 10^9/L.

If a patient experiences an ANC < 1.5 x 10^9/L or a platelet count < 100 x 10^9/L while on treatment with IFN-a alone confirmed by two consecutive readings one week apart the dose of IFN-a should be reduced to 25%.

If a patient experiences an ANC < 1.0 x 10^9/L or a platelet count < 50 x 10^9/L while on treatment with IFN-a alone IFN-a should be withheld and the dose reduced to 50% after ANC recovery to ≥ 1.5 x 10^9/L and platelet recovery to ≥ 100 x 10^9/L.

/s/

Ann Staten
4/11/01 02:20:29 PM

Richard Pazdur
4/11/01 02:36:58 PM

TELECON MINUTES

MEETING DATE: Dec. 7, 1999 **TIME:** 10:30 **LOCATION:** C

IND: [redacted] **Meeting Request Submission Date:** 10-29-99
Briefing Document Submission Date: 11-5-99
Additional preparation documents: 11-19-99 fax

DRUG: STI571 **SPONSOR:** Novartis **TYPE of TELECON:** EOP1/2 for chronic myelogenous leukemia

FDA PARTICIPANTS: Richard Pazdur, M.D., Dir., HFD-150
Rachel Behrman, M.D., Dep. Dir., HFD-101
John Johnson, M.D., Medical Team Leader, HFD-150
Marty Cohen, M.D., Medical Officer, HFD-150
Mark Rothmann, Ph.D., Statistician, HFD-150
Dotti Pease, Project Manager, HFD-150 (for Ann Staten)

INDUSTRY PARTICIPANTS:
Ellen Cutler, Drug. Reg. Affairs
Manuel Litchman, M.D., Clin. Research
Guenther Mehring, Ph.D., Clin. Pharm.
David Parkinson, M.D., Clin. Research
Bin Peng, Ph.D., Clin. Pharm.
Elisabeth Wehrle, Ph.D., Biostat.
Brian Druker, M.D., Oregon Health Sciences University, Portland, OR

MEETING OBJECTIVES: Discuss FDA responses to sponsor's questions (attached). These had been faxed to sponsor on 12-2-99.

BACKGROUND:

Novartis presented an update on the clinical plan for CML, which they propose to be a 3-prong approach studying various patient groups as follows:

- myeloid blast crises (protocol 102)
- accelerated phase (protocol 109)
- interferon-unresponsive patients (protocol 110)

plus, a randomized trial of front line treatment in CML to start at the end of 2000. This trial would have 3-4 arms (STI vs. STI/INF vs. Ara-C /INF)

DISCUSSION:

1. (2.a.)Discussion began with the proposed definition of "interferon-refractory," which sponsor agreed was not accurate and suggested revising to "interferon-unresponsive." The FDA believes patients should have progressed on interferon to be eligible. Patients who are stable on interferon may still be benefiting from interferon. Agreement was not reached on this definition.

2. (1.a. and 3.)FDA explained that under the accelerated approval regulations a surrogate, such as cytogenetic response) must be reasonably likely to predict survival. Hematologically progressing patients, if properly defined, might be a more appropriate group to study, with cytogenetically progressing patients studied separately. FDA questioned why randomized trials were not being done. Sponsor replied that a) there is no effective control and b) the sponsor believes patients won't accept randomization as they all want STI571. In the sponsor's opinion, Hydrea is not considered an effective control and is only used to "keep the lid on things" whereas STI571 is causing durable responses.

   FDA questioned what Novartis plans to conduct for a confirmatory clinical trial, assuming that the do pursue a path toward accelerated approval. Novartis proposed a randomized controlled trial in patients receiving initial treatment for CML. The arms are still under discussion, but would probably be STI alone versus STI + Interferon versus Ara-C + Interferon. In response to FDA's question re: why the randomized trial isn't starting sooner than the end of the year 2000, Novartis noted that the have not been done yet. FDA pointed out that Novartis is trying to answer too many questions in one study and suggested a study of STI vs. Ara-C/INF with endpoints of delay in time to accelerated phase or blast crisis, noting that these are acceptable clinical endpoints and the sponsor is not obligated to study only survival. If the results were as spectacular as postulated, a large number of patients would not be needed. This design would allow us to determine the role of STI in this disease more quickly than the proposed three arm RCT .

ACTION ITEMS:

1. All three protocols will be revised and resubmitted by the beginning of January, including the randomized trial protocol.

2. Protocol 110 will be revised to refer to patients who are "interferon-unresponsive," and Novartis will provide data supporting the definition. Sponsor will also amend protocol 110 to add hematologic failures and to document the rationale for studying cytogenetic failures. This study has already started enrollment, so statistics will have to be adjusted also. FDA will be looking mainly at hematologic progression. This revised protocol will be submitted within a day or two.

3. FDA will review these protocols and meet with Novartis by the end of January (Ann to schedule meeting immediately).

/S/ /S/

Dotti Pease, Project Manager

Concurrence Chair:
Martin Cohen, M.D.
Medical Reviewer

ATTACHMENT: Questions and FDA Answers Faxed to Sponsor 12-2-99

cc: ORIG. IND
Div. File
Attendees electronically
HFD-150/DWPease/ 12-13-99/rev. 12-15-99 per RB and JJ/12-21-99 final typed

MEETING MINUTES

The proposed trial is a phase II, non-randomized evaluation of ST1571an inhibitor of the protein-tyrosine kinases associated with Bcr-Abl in CML patients who are refractory to or are intolerant of IFNα. The major issues in this trial are 1) that it is non-randomized, 2) that it uses definitions of IFN refractory disease that are not universally accepted, and 3) that it will provide little useful information regarding time-to-event endpoints.

The sponsor's stated reason for the non-randomized design is because of the poor activity of hydroxyurea as either first- (<5% major cytogenetic responses) or second-line therapy. In addition, the ongoing Phase I study with STI571, doses of 300 to 600 mg administered daily have induced CHR's in 31 of 31 patients (100%). With only limited follow-up of the 22 patients treated at doses of 300 to 500 mg of STI571, major and minor cytogenetic responses have already been documented in 2 (9%) and 9 (41%) patients, respectively.

The above reasoning is logical but there are major problems with definitions of IFN refractory and intolerant disease. Patients defined as IFN refractory really have stable disease. The definition of intolerance suggests that only a relatively low percent of treated patients would qualify.

A further issue is that the sponsor's primary endpoint is cytogenetic response. Whether cytogenetic response is a surrogate for clinical benefit is uncertain.

Sponsor's Questions

1. a. Given the lack of alternative efficacious therapeutic options in patients with interferon-refractory CML, would the proposed study support the registration of STI571 in patients with CML refractory to interferon?

FDA Response:

No. You appear to be seeking accelerated approval of STI571. You have not established that cytogenetic response is an adequate surrogate for clinical benefit and that this population is refractory to available therapy. We strongly recommend that you consider a randomized controlled trial examining accepted endpoints of clinical benefit, e.g., delay in time to accelerated phase or blast crisis.

b. Would concordant data from the interferon-intolerant cohort support a broader indication to encompass this population?

FDA Response: No.

2. a. Do you concur with the definition of interferon-refractory as detailed in the inclusion criteria?

FDA Response:

No.

The protocol definition of refractory includes patients with stable disease but who do not demonstrate a cytologic or hematologic response. Standard care would be to continue INF treatment until clinical disease progression (an accelerated phase).

b. Do you concur with the definition of interferon-intolerant as detailed in the inclusion criteria?

FDA Response:

No

Definition of interferon-intolerant is vague. There is no indication that interventions aimed at decreasing toxicity, e.g., ancillary medications, psychosocial support etc were optimally used.

3. Do you agree with the inclusion of major cytogenetic responders (1-35% Ph+ chromosome cells) in the definition of response?

FDA Response:

See our response to 1a.

4. For the registration package, we intend to follow all patients in study 0110 for a minimum of six months. Is this follow-up sufficient to demonstrate durability of response?

FDA Response:

No

Durability might be missed if follow-up was limited to 6 months. The literature indicates that for patients with CHR the median time to CCyR is 9-18 months.

5. The NDA will include data on approximately 100 patient electrocardiograms (EKGs) and urinalyses obtained at baseline and at the end of study from the Phase I study, and all patients will have EKGs at baseline, steady state and end of study in protocol 0110.

   a. Do you concur that the extent of these evaluations is sufficient for registration?

   FDA Response:

   Please clarify the above. The agent doesn't appear to have any cardiac or renal toxicity.

   b. Given the relatively limited size of the safety database, is there a need to collect any additional safety information (e.g., chest X-rays)?

   FDA Response:

   See above

Additional FDA Comments:

<u>Clinical Pharmacology and Biopharmaceutics</u>

1. **Please provide a protocol/analysis plan of the population pharmacokinetics portion of the study.**

2. **Please provide the rationale for STI571 being administered in the morning two hours following breakfast.**

3. **It is unclear what day of the dosing regimen the sparse sampling technique will be utilized.**

   At this time the protocol states that sampling will take place on day 1 and 29 of the dosing regimen. However, the protocol also states that sample collection of the sparse sampling regimen is at the convenience of the patient. Please clarify.

4. **Please provide the rationale for the full-sample profile schedule.**

   Currently the sponsor intends to sample out to possibly one t½ (24 hours). STI571 has a t½ of 10 to 23 hours making the sampling regimen inadequate for a full profile assessment (out to 3 t½).

MEETING MINUTES

MEETING DATE: June 15, 1999 **TIME:** 9:30 am-11am **LOCATION:** Conference Room E

IND/NDA IND [redacted] Meeting Request Submission Date: April 21, 1999
Briefing Document Submission Date: May 14, 1999; June 8, 1999.
Related Submissions: May 19, 1999 (Fast Track Request)

DRUG: STI571 (formerly CGP 57148B)

SPONSOR/APPLICANT: Novartis Pharmaceuticals Corporation

TYPE of MEETING:

1. End of Phase 1 / End of Phase 2

2. **Proposed Indication:**
   1. Treatment of patients with CML in blast cell crisis.
   2. Treatment of patients with advanced Ph chromosome positive leukemias.

FDA PARTICIPANTS:
Robert Temple, M.D., Office Director, Office of Drug Evaluation I (internal meeting only)
Rachel Behrman, M.D., MPH, Office Deputy Director, Office of Drug Evaluation I
Robert Justice, M.D., Acting Director, Division of Oncology Drug Products
Julie Beitz, M.D., Acting Deputy Director, Division of Oncology Drug Products
Ken Kobayashi, M.D., Medical Reviewer
John Johnson, M.D., Medical Team Leader
Paul Andrews, Ph.D., Pharmacology/ Toxicology Team Leader (industry meeting only)
Sandip Roy, Ph.D., Acting Pharmacology/ Toxicology Team Leader (internal meeting only)
Ann Staten, RD, Project Manager
Gang Chen, Ph.D., Biometrics Team Leader (internal meeting only)
Clara Chu, Ph.D., Biometrics Reviewer
Elena Mishina, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Atiqur Rahman, Ph.D., Clin. Pharm. and Biopharm., Team Leader (internal meeting only)
Sung Kim, Ph.D., Chemistry Reviewer
Janice Dutcher, M.D., ODAC consultant (internal meeting only)

INDUSTRY PARTICIPANTS:
Philip Bentley, Ph.D., Preclinical Safety
Ellen Cutler, Regulatory Affairs
John M. Ford, M.D., Clinical Development
David Parkinson, M.D., Clinical Development
Debra Resta, Clinical Development
Elisabeth Wehrle, Ph. D., Biostatistics
Sharon Olmstead, Regulatory Liason
Brian Druker, M.D., Consultant, Oregon Health Science Center

IND

MEETING OBJECTIVES:

1. To obtain the Division's feedback regarding the adequacy of Novartis' proposed program to support the registration of STI571 for the treatment of patients with chronic myeloid leukemia in myeloid blast crisis.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Novartis made a presentation to update the Agency (see attached slides).

Preclinical

1. An overview of the preclinical toxicology program is provided in the attached Investigators' Brochure. In addition to the completed program, 13-week rat and monkey toxicity studies are ongoing. Twenty six-week rat toxicity and 39-week monkey toxicity studies are planned. We believe this program is adequate to support registration for patients with chronic myeloid leukemia (CML) in myeloid blast crisis. Do you concur?

FDA Response:

- Yes, this is adequate, however, a 26 week monkey study may also suffice rather than a 39-week monkey study. Factors to consider in attempting to justify a 26 week study are: a) the comparability of human toxicities to rodents and non-rodents; b) the comparability of human pharmacokinetics to rodents and non-rodents; and c) the experience with long term use in humans in Phase 2 and 3 clinical studies.

2. On the basis that STI571 will be indicated for patients with chronic myeloid leukemia we do not plan to conduct carcinogenicity studies to support registration. Is this acceptable?

FDA Response:

- Yes.

Clinical Pharmacology

3. Is the clinical pharmacology program described in Section 5.1 adequate to support the registration for chronic myeloid leukemia in myeloid blast crisis? Additional pharmacokinetic studies (drug and food interactions, absolute bioavailability studies) are planned for after the initial registration.

FDA Response:

- The Clinical Pharmacology and Biopharmaceutics program is not adequate. Absolute or relative bioavailability information is required for NDA filing for an oral agent according to CFR 320.25.

- Is there any reason why this can not be done prior to the submission of the NDA?

Novartis Response:

- No, we will provide absolute and relative bioavailability with the filing of the NDA.

Clinical Development

4. Registration program for patients with chronic myeloid leukemia in myeloid blast crisis:

   a. Given the absence of effective standard therapy for the treatment of patients with CML in myeloid blast crisis, we believe a single uncontrolled trial should be adequate to support registration, provided that, in the absence of major safety issues, an acceptable degree of efficacy is demonstrated. Would the proposed study 0102 with support from approximately 30 patients with CML in blast crisis from study 001 support registration of STI571 for treatment of patients with CML in myeloid blast crisis?

FDA Response:

To be eligible for accelerated approval (21 CFR 314.500, Subpart H), the treatment must represent a therapeutic gain that provides "meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)."

There is no standard therapy for patients with accelerated phase CML or CML in blast crisis, although a number of regimens have been utilized and studied, including "AML induction-like regimens", carboplatin, and hematopoietic stem cell transplantation – allogeneic and autologous. Long-term survivorship is reported with transplantation (20-40% four year survival in accelerated phase; 10-15% "long-term" in blast crisis), and high response rates (>30% CR for blast crisis) have been reported with the "AML induction-like regimens".

It is not clear, given the data submitted thus far and the target CR rate of 20%, that the phase 2 experience contemplated would provide evidence that STI571 would provide a therapeutic gain over available therapy. A high CR rate with durable remissions in a single-arm trial could be sufficient for accelerated approval for blast crisis and if dramatic enough, might qualify for traditional approval. As you plan the trial, note that it would be important to document improvement in symptoms.

Survival data from a phase 2 trial is generally not interpretable and cannot be compared in a meaningful fashion to survival data derived from the reports of other studies.

Given the concerns we have already stated, an adequate and well-controlled phase 3 trial is recommended. A randomized, controlled trial would not only clarify the comparisons of toxicity and response data, but would provide a setting for generation of meaningful survival data.

Early response/toxicity data from the phase 3 trial could potentially serve as grounds for accelerated approval, with the survival data, if persuasive, supporting subsequent full approval. If the survival data is not sufficiently persuasive, evidence of clinical benefit from another trial(s) may be needed to support the application for full approval. A randomized phase 3 trial in MDS or in early chronic phase disease could be supportive.

IND .

Study 0001 can most usefully contribute if the 30 patients being proposed are treated at the same dose level (or at most, balanced between 2 levels) and if careful documentation of the degree of response, including bone marrow and cytogenetic studies, is obtained.

The Medical Review comments regarding study 0102 which will be attached to your copy of the meeting minutes.

b. Would data from study 0107 support a broader indication to include patients with advanced Ph chromosome positive leukemias?

FDA Response:

- It is difficult to answer because we do not have sufficient information to comment. It is possible if the CR rates are sufficiently high and durable .

5. No effective standard therapies are available for the treatment of these patients and therefore it is difficult to define a suitable control arm. However, the natural history of this disease is well defined and the life expectancy is predictably short. Under these circumstances, it is reasonable to use historical data sets in order to evaluate potential therapeutic benefit. Do you concur with this proposal?

FDA Response:

- Maybe.

6. The proposed primary endpoint is the proportion of patients achieving a complete hematological response or chronic phase hematopoiesis lasting for $\geq$ 12 weeks. Secondary end-points will include overall survival, cytogenetic responses and quality of life parameters. Are these outcome measures acceptable?

FDA Response:

- The outcome measures will need to be clearly defined in the protocol.
- See response to question 4.
- The proposed endpoint is a composite. CHR and reversion to chronic phase hematopoeisis should also be reported separately. This endpoint will be more convincing in a randomized controlled study than in a single-arm non-comparative study. We suggest that you look at the response definitions used in recent cooperative group CML studies.
- All clinical parameters should be evaluated (e.g., splenomegaly, lymphadenopathy, transfusion requirements, infection, etc.)

Novartis Response:

We are no longer planning a formal QOL assessment.

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7. [redacted]

FDA Response:
Pediatric Exclusivity:

We suggest that you develop a proposal for pediatric studies in the form of a Proposed Pediatric Study Requirement (PPSR) and submit it for our review.

Please refer to the "Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act" at Drug Information Branch (301) 827-4573 or http://www.fda.gov/cder/guidance/index.htm.

Pediatric Final Rule:

Please note that you will need to address the December 2, 1998 Pediatric Rule (63 FR 66632) when you submit your NDA unless your product/indication has been designated an Orphan Drug. You may be eligible for a waiver under 21 CFR 314.55 (c).

Registration program for patients with early chronic CML:

8. Registration of STI571 for the treatment of CML in early chronic phase will require a randomized trial against standard therapy (currently interferon alpha), with survival as the ultimate endpoint. Such a trial would take many years to complete given the incidence of CML and its relatively long natural history. It may be reasonable to consider Accelerated Approval based on a composite endpoint such as proportion of complete hematological responders, proportion of major cytogenetic responders and possibly the relative toxicity profiles (in the event that STI571 is given as a single agent) while awaiting the outcome of survival. Do you concur with this proposal?

FDA Response:

- Superiority over IFN in an endpoint defined as:
  - Normalization of peripheral counts; and
  - <5% blasts in bone marrow

  in the same patient, may support accelerated approval.

Novartis Response:
- Novartis concurs.

Comment on Compassionate Use protocol:

If drug supply is so limited, why not use the patients in study 0107?

Novartis Response:
- We intend to direct eligible patients to the appropriate center.

Fast Track Designation

9. We have submitted a request for Fast Track designation. A possible consequence of a rapid clinical development program is that the technical development program may lag behind. We will request a CMC meeting to discuss the implications in detail. Specifically, will Fast Track designation allow for flexibility in the submission of stability data in the CMC documentation of the NDA submission?

FDA Response:
Although it will be considered, Fast Track designation does not reduce CMC requirements. Please note that enough stability data is needed to assess a proposed expiration dating period during the NDA review process.

Novartis Response:
We will request a CMC meeting as development plans continue.

Financial Disclosure

10. We propose to submit the appropriate Financial Disclosure certification in accordance with the Final Rule published in the December 31, 1998 Federal Register for all investigators who enroll patients in Studies 001 (ongoing as of February 2, 1999), 0102, 0103 and 0107. These studies are the basis for establishing the safety and efficacy of STI571 for the proposed indication of chronic myeloid leukemia in myeloid blast crisis. Is this acceptable?

FDA Response:
Yes. We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective, or that makes a significant contribution to demonstration of safety.

Please refer to the provided copy of the "Financial Disclosure by Clinical Investigators Final Rule Summary".

IND

FDA Comments regarding protocol 0102:

The following comments and requests for information were provided to the sponsor but not discussed at the meeting.

- Regarding section 2, "Study Objective": The study objectives should state the primary and secondary endpoints.
- Regarding section 3.3.2, "Inclusion and Exclusion Criteria":
  - Other recently published studies in CML blast phase have included cytogenetic criteria in defining blast phase, as well as information from other cell lineages. Please clarify whether the protocol definition of blast crisis will include such elements.
  - The phrase "no prior AML type therapy as treatment for blast crisis" is vague and should be made more explicit.
  - The renal function and bilirubin criteria should be stated more clearly and the renal function criterion should be tightened.
  - The exclusion criteria should include reference to serious concomitant medical conditions; this might include history of peptic ulcer disease, GI bleed, etc. in view of the reported GI bleed on the phase I study.
- Regarding section 3.4.3, "Concomitant Medications/Non-Drug Therapy": The use of leukapheresis may be a potential confounder in evaluating efficacy outcomes and its use should be more clearly defined. Furthermore, the handling of such patients in the analysis should be addressed.
- Regarding section 3.5.1, "Efficacy Assessments": The outcome criteria should be more clearly defined. For instance, the statement "A peripheral blood picture compatible with chronic phase CML, in the absence of features compatible with accelerated phase, will also be regarded as a response." should be more specifically defined.
- Regarding section 3.5.1, "Efficacy Assessments": Survival and quality of life measures are cited by the sponsor as being secondary endpoints in the cover letter, but no mention of these measures are made in the protocol. The protocol must include the definitions, instruments to be used, data collection procedures, and analytic plans for these endpoints.
- Regarding section 3.5.1, "Efficacy Assessments": If the study is to be conducted in multiple centers, then will the cytogenetic material and bone marrow morphologies be centrally reviewed? If the study is to be a single center study, then we suggest that the cytogenetic material and bone marrow morphologies be evaluated by an examiner independent of the study.
- Regarding section 3.5.1, "Efficacy Assessments": As a suggestion, not a requirement, the sponsor may wish to include molecular assessments of the bcr-abl rearrangement and pharmacodynamic assessments of the bcr-abl gene expression, considering the postulated mechanism of action of this drug.
- Regarding section 3.5.1, "Visit Schedule and Assessments": The diagram should be made consistent with the text.
- Bone marrow cytogenetics should be evaluated at baseline.

IND

- Regarding section 3.1, "Overall Study Design": The protocol states that 59 patients will be accrued, but the cover letter states that 89 patients will be accrued. Please clarify the intended sample size.

ACTION ITEMS:

1. Novartis will submit a revised protocol for study 0102 for the Agency to review.
2. Novartis will provide absolute and relative bioavailability with the filing of the NDA.
3. Novartis will request a CMC meeting as development plans continue.

The meeting was concluded at 10:30am. There were no unresolved issues or discussion points.

/S/ 7-19-99

Ann Staten, RD Date
Project Manager
Minutes preparer

Concurrence Chair. /S/ 7/21/99

Keri Kobayashi, MD Date
Medical Officer

Attachments: Overall Clinical Development Plan (briefing book submitted 5-14-99); Novartis overheads from the opening presentation; "Financial Disclosure by Clinical Investigators Final Rule Summary".

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-335 /SE1 - 004

Drug Gleevec (imatinib mesylate) Applicant Novartis

RPM Ann Staten Phone 301-594-0490

■505(b)(1)
☐505(b)(2) Reference listed drug

☐Fast Track ☐Rolling Review Review priority: ☐ S ■P

Pivotal IND(s) ( )

Application classifications:
Chem Class 1PV (new indication)
Other (e.g., orphan, OTC) Orphan designation received after NDA submission

PDUFA Goal Dates:
Primary December 28, 2002
Secondary

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ■ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ■AP ☐ AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... X agreed upon version dated
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling..... N/a
  Has DDMAC reviewed the labeling? ..... ■ Yes (include review) ☐ No
  Immediate container and carton labels ..... N/a
  Nomenclature review ..... N/a

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ■ is not on the AIP.
  Exception for review (Center Director's memo)..... N/a
  OC Clearance for approval..... N/a

- Status of advertising (if AP action) ■ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter

- Post-marketing Commitments
  - Agency request for Phase 4 Commitments X
  - Copy of Applicant's commitments X

- Was Press Office notified of action (for approval action only)? ..... ■ Yes ☐ No
  - Copy of Press Release or Talk Paper ..... N/a

- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)] ..... N/a
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] ..... N/a

- Exclusivity Summary X

- Debarment Statement X

- Financial Disclosure
  - No disclosable information X
  - Disclosable information – indicate where review is located ..... N/a

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings X
  - Date of EOP2 Meeting 6/15/02;12/7/99;5/3/00; 8/31/00
  - Date of pre NDA Meeting 3/26/02
  - Date of pre-AP Safety Conference N/a

- Advisory Committee Meeting ..... 11-7-02 (individual consultants)
  - Date of Meeting ..... N/a
  - Questions considered by the committee ..... N/a
  - Minutes or 48-hour alert or pertinent section of transcript ..... N/a

- Federal Register Notices, DESI documents ..... N/a

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g.. Office Director's memo, Division Director's memo, Group Leader's memo) ..... Pharm/Tox 12-16-02

- Clinical review(s) and memoranda X
- Safety Update review(s) ..... N/a
- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... ~~Orphan Drug~~ Designation
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ■Not Applicable
- Statistical review(s) and memoranda X
- Biopharmaceutical review(s) and memoranda..... X
- Abuse Liability review(s) ..... N/a
  Recommendation for scheduling ..... N/a
- Microbiology (efficacy) review(s) and memoranda ..... N/a
- DSI Audits X
  ☐Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- CMC review(s) and memoranda X
- Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/a
- DMF review(s) ..... N/a
- Environmental Assessment review/FONSI/Categorical exemption ..... X- see CMC review
- Micro (validation of sterilization) review(s) and memoranda ..... N/a
- Facilities Inspection (include EES report)
  Date completed N/a ..... ☐ Acceptable ☐ Not Acceptable
- Methods Validation ..... ☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Pharm/Tox review(s) and memoranda ..... X Dated 12-16-02

- Memo from DSI regarding GLP inspection (if any) ..... N/a
- Statistical review(s) of carcinogenicity studies ..... N/a
- CAC/ECAC report ..... N/a

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	**ODS POSTMARKETING SAFETY REVIEW**	
FROM: DDRE (HFD-430) Kathleen Phelan, R.Ph., Safety Evaluator	**DATE:** October 11, 2002 **ODS PID #** D020416	
TO: Richard Pazdur, M.D., Director, HFD-150, DODP	**THROUGH:** Julie Beitz, M.D., Director, HFD-430, DDRE	
DRUG (Est)/APPROVAL: imatinib mesylate/May 10, 2001	**NDA #** 21-335	**SPONSOR:** Novartis
DRUG NAME (Trade): Gleevec	**THERAPEUTIC CLASSIFICATION:** cytotoxic	
EVENT: cerebral edema and papilledema		

Executive Summary:

Reports of papilledema and cerebral edema associated with imatinib were noted during routine AERS in-box review. Imatinib is labeled for severe fluid retention and edema outside of the CNS. AERS and literature searches identified three cases of papilledema and two cases of cerebral edema that are possibly related to imatinib use in patients with chronic myelogenous leukemia (CML). The edema occurred during imatinib use, etiologies were not determined, and, in four cases, edema resolved with imatinib discontinuation alone or with imatinib discontinuation and other treatment. The fifth case resulted in death and an autopsy found cerebral edema with no evidence of CNS leukemic infiltration or hemorrhage. There was one case each of cerebral edema and papilledema in which imatinib was restarted without recurrence of the edema noted at the time of reporting.

Because of the clinical consequences of increased intracranial pressure, which is associated with both papilledema and cerebral edema, we recommend that papilledema and cerebral edema be added to imatinib labeling to alert health care professionals to these possibilities.

Reason for Request/Review:

During routine AERS in-box review, I noticed reports of papilledema and cerebral edema that had no medical explanation in patients taking imatinib. Because imatinib is associated with edema and with serious fluid retention, such as pleural effusion, it seemed possible that imatinib might also be associated with papilledema and cerebral edema. Thus, this review explores papilledema and cerebral edema possibly associated with imatinib.

Relevant Product Labeling:

Precautions, General

Fluid Retention and Edema:

DRAFT

%

Literature Search

Search Date: August 27, 2002	**Search Type:** PubMed

Search Criteria: three separate searches - imatinib edema, imatinib papilledema, imatinib/AE (AE=adverse events)

Search Results:

One report of two cases of cerebral edema was found.[1] One of these cases is also in AERS. Both cases are summarized below with the AERS search results.

AERS Search

Search Date: August 6, 2002

Search Criteria:

Drug names: imatinib mesylate, imatinib, Gleevec

MedDRA search terms: HLGT level – Increased intracranial pressure and hydrocephalus

PT level – CSF pressure increased, CSF pressure abnormal nos

Search Results:

Total AERS reports for imatinib on September 3, 2002 was 716.

This search retrieved 7 unduplicated cases. One additional AERS case was received August 15. Addition of the literature case not in AERS makes a total of 9 unduplicated cases.

Inclusion/exclusion criteria: Cases were accepted as possible papilledema or cerebral edema associated with imatinib if papilledema, increased intracranial pressure, or cerebral edema was reported in a patient during or shortly after imatinib treatment and investigations found no explanation for the event, such as evidence of CNS hemorrhage or leukemic CNS infiltration.

Search Results continued:

5 accepted cases: 4 AERS cases and 2 literature cases, 1 of which is also in AERS

- 1 bilateral papilledema with normal brain MRI and normal lumbar puncture but no measure of intracranial pressure
- 2 bilateral papilledema with increased intracranial pressure documented by lumbar puncture from the same reporter
  2 cerebral edema from the same published article[1]

4 excluded cases

- cerebral edema and increased intracranial pressure ruled out as causes of CNS symptoms
- CNS leukemia
- subdural hemorrhage
- veno-occlusive disease and massive hepatic necrosis per autopsy account for increased intracranial pressure

Summary of accepted case series

For summaries of individual cases and more detailed information, see *Attachment 1 – Case Summaries.*

Patients in the five accepted cases comprise three males and two females ranging in age from 33 to 68 years with mean and median ages of 53 2 and 59 years, respectively. All were receiving imatinib to treat chronic myeloid leukemia (CML), one newly diagnosed in chronic phase, one in accelerated phase, two in blast crisis, and one not further specified. Imatinib dosages were all within labeled recommendations and ranged from 400 to 800 mg per day, with both mean and median dosages of 600 mg per day. Medical histories were not reported in three cases, but included diabetes mellitus, interstitial lung disease, and controlled hypertension in one case and post-herpetic neuralgia in the remaining case. Concomitant medications were not reported in four cases. For concomitant medications in the remaining case, see the last case on *Attachment 1 - Case Summaries.* Times to onset ranged from 2 to 28 months, with a mean of 8 9 months and a median of 6 months The reported adverse events are bilateral papilledema diagnosed by ophthalmologic exam in three cases, with increased intracranial pressure diagnosed by lumbar puncture in two of these three cases, cerebral edema diagnosed by MRI and CT in the fourth case, and cerebral edema diagnosed by autopsy in the fifth case. Four cases resolved: after imatinib discontinuation and steroid treatment in two cases, after imatinib discontinuation and acetazolamide treatment in one case, and after imatinib discontinuation alone in one case. In two cases, imatinib was restarted without a recurrence of the adverse event at the time of reporting. The fifth case resulted in death. No evidence of intracranial hemorrhage or leukemic infiltration of the CNS was found in any of the five accepted cases. Both MRIs and lumbar punctures were performed in the four nondeath cases and autopsy was performed in the death case.

Discussion / Conclusions:

This series of five cases represents increased intracranial pressure as papilledema or cerebral edema. These cases occurred in patients being treated for CML with labeled doses of imatinib. One case resulted in death with cerebral edema determined as the main cause. All cases occurred during imatinib use, three resolved with treatment and imatinib discontinuation, and one resolved with imatinib discontinuation alone. In no case was an etiology determined. Leukemic infiltration and hemorrhage were ruled out as possible causes of papilledema or cerebral edema by MRI or lumbar puncture in four cases, and by direct brain tissue examination in the fifth case. Thus, these cases are consistent with an association between imatinib and papilledema or cerebral edema. Two patients reinitiated imatinib without a recurrence of the adverse event by the time of reporting

The authors of the literature report of two cerebral edema cases suggest a role for imatinib in producing edema through inhibition of the platelet-derived growth factor (PDGF) receptor. They state that imatinib was originally developed as a PDGF-receptor inhibitor and that this receptor regulates interstitial fluid pressure. They further state that inhibition of the PDGF receptor has been associated with fluid retention.[1]

Imatinib is labeled for edema and fluid retention at sites outside of the CNS. We have presented five cases of papilledema or cerebral edema occurring temporally to imatinib use with no alternative explanation for the edemas. Thus, an association between imatinib and papilledema and cerebral edema is possible. Because of the clinical consequences of increased intracranial pressure, which is associated with both papilledema and cerebral edema, we recommend that papilledema and cerebral edema be added to imatinib labeling to alert health care professionals to these possibilities.

Reviewer's Signature / Date:	**Team Leader's Signature / Date:**

Division Director Signature / Date:

Reference:

1. Ebnoether M, Stentoft J, Ford J, et al. Cerebral oedema as a possible complication of treatment with imatinib. Lancet 2002 May 18; 359:1751-2.

Attachments:

Attachment 1 - Case Summaries

Attachment 1 - Case Summaries

ISR# 3945490-3, MFR# PHHO2000CH08138, foreign, 2000, cerebral edema
Lancet 2002 May 18; 359:1751-2

A 61-year-old female with CML began treatment with imatinib 600 mg per day in January, 2000 for lymphoid blast crisis as part of a phase II study. Complete hematological and cytogenetic response was achieved after 3 months. In July, 2000, she developed headache, nausea, and vomiting. Cerebral MRI was normal at that time. In September, massive cerebral edema was diagnosed by CT and MRI. CSF analysis was inconclusive, but there was no radiological evidence of leukemia in the CNS. Imatinib was discontinued and symptoms resolved with dexamethasone treatment. Six weeks later, after the patient developed paraplegia, lymphoid disease in the CNS was diagnosed by CT and cytological and immunophenotyping of cells in the CSF. After remission was achieved, imatinib was restarted at 300 mg per day and increased to 800 mg per day without recurrence of cerebral edema.

Lancet 2002 May 18; 359 1751-2, cerebral edema

A 68-year-old male with CML began treatment with imatinib 600 mg per day in November, 2000, for myeloid blast crisis as part of a phase II study. A partial clinical response, which included reduction in hypermetabolic symptoms, splenomegaly, and leukocyte count, was achieved, followed by pancytopenia After 4 weeks of imatinib use, the patient developed nausea, vomiting, and abdominal pain, which resolved with imatinib discontinuation. Imatinib was restarted at 400 mg per day in December 2000, but nausea and vomiting returned. Imatinib was discontinued on January 5. The patient developed paresis and lost consciousness on January 11, and died 2 days later Autopsy determined cerebral edema as the main cause of death. Autopsy showed coning, stasis, and extravasation. Histological assessment showed stasis with a few perivascular hemorrhages, diffuse edema of the cortex, and pontine hemorrhages cranial to the fourth ventricle. No evidence of leukemia was found in the CNS.

ISR# 3735055-0, MFR# PHEH2001US04184, U S , 2001, papilledema*

A 33-year-old male began treatment with imatinib 400 mg per day on November 7, 2000 for previously untreated CML in chronic phase as part of a phase III study. On May 5, 2001, bilateral macular edema and increased intraocular pressure were noted on a routine eye examination. Lumbar puncture on an unspecified date showed a pressure of 27 cm H_2O and negative cytology. MRI and MR venogram were normal. Intracranial hypertension of unclear etiology was diagnosed. Imatinib was discontinued on May 9 and the adverse events resolved. Therapy was changed to interferon with no further problems.

SR# 3965221-0, MFR# PHEH2002US07038, U S., 2002, papilledema*

A 59-year-old female with a history of post-herpetic neuralgia participated in a study of imatinib as treatment for CML from March 8, 1999 until April 11, 2002 On April 12, 2002, she began treatment with commercial imatinib 800 mg per day. Because of headaches and eye pain, an ophthalmological exam was performed on July 16. "Minimal fullness of optic discs" was found. MRI was normal. Slit-lamp examination on July 19 showed flat subconjunctival hemorrhages in the right eye and trace nuclear sclerotic cataracts on both eyes. Lumbar puncture on July 26, performed because of headaches and papilledema, revealed an opening pressure of 30 cm H_2O, diagnosed as increased intracranial pressure, grade three. Imatinib was discontinued on July 29, acetazolamide treatment was initiated, and the patient recovered.

ISR# 3828310-7, MFR# PHEH2001US04940, U.S., 2001, papilledema**
ISR# 3735588-7, Direct report, U.S., 2001**

A 45-year-old male began treatment with imatinib 600 mg per day on March 31, 2001 for CML in accelerated phase as part of an open-label study. Concurrent medical conditions included diabetes mellitus, interstitial lung disease, and hypertension, with a current blood pressure of 140/63. Concomitant medications were dexamethasone, rifampicin, pirazinamide, allopurinol, insulin, ipratropium and albuterol. Imatinib was not administered on May 17 but was resumed at 400 mg per day on May 18. On May 20, after the patient complained of loss of vision in his right eye, an ophthalmological exam revealed bilateral papilledema. On May 25, MRI found no evidence of abnormal intracranial space-occupying lesion and optic nerve roots appeared normal. Extraocular muscles of both orbits appeared prominent, however. Study imatinib was discontinued. On May 26, leukocyte, erythrocyte, and platelet counts were below normal at 1.9 x 10^9/L (normal 4.0-11.0), 2.8 x 10^{12}/L (4.7-6.1) and 14 x 10^9/L (130-140), respectively. Hemoglobin was 8.8 g/dL (normal 14.0-18.0) and hematocrit was 24.3% (42-52). Alkaline phosphatase was slightly elevated (value not provided). Because of grade III thrombocytopenia, lumbar puncture was delayed until May 28. The results were normal but intracranial pressure was not measured. The patient recovered with discontinuation of imatinib and intravenous steroid treatment. On June 1, the patient was discharged from the hospital on commercial imatinib without a recurrence of papilledema.

* These two cases are from the same reporter.

** These two reports share state of origin and patient age, gender, and initials. Also, dates of imatinib initiation and adverse event recurrence are very close, as are concomitant illnesses. Although other details differ and the reporter of the direct report denied in follow-up that the patient was participating in a trial, the data are blended into one case.

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

/s/

Kathleen Phelan
10/11/02 04:56:39 PM
PHARMACIST

Julie Beitz
10/15/02 10:13:26 AM
DIRECTOR

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commercial

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Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Mr. Peter Tough, Head Coordinating Section, Drug Safety and Evaluation Branch

From: Ann Staten, Project Manager

Fax: 61 2 6232 8140 **Fax:** 301-827-4590

Phone: 61 2 6232 8047 **Phone:** 301-594-0490

Pages: 21 4 of 5 **Date: December 20, 2002**

Re: Gleevec Medical Review – provided in confidence

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

- **Comments:**

Dear Mr. Tough,

Please find attached a copy of the Gleevec review, provided to your agency in confidence, per the request of Mr. McGinness.

Please let me know if you receive this in it's entirety and if you or your team has any questions.

Sincerely,

Ann Staten, RD
Project Manager

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No 0910-0297
Expiration Date February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U S mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website. http://www fda gov/cder/pdufa/default htm

1 APPLICANT S NAME AND ADDRESS

Novartis Pharmaceuticals Corporation
One Health Net Plaza
East Hanover, New Jersey 07936

2 TELEPHONE NUMBER *(Include Area Code)*

(973) 781-6940 - Vera Wolsch

4 BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-335

5 DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO CONTAINING THE DATA)

3 PRODUCT NAME

Gleevec ™ (imatinib mesylate) Capsules

6 USER FEE I D NUMBER

4367

7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☒ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug and Cosmetic Act
(See item 7, reverse side before checking box)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO

(See Item 8 reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Robert A Miranda	Director, Drug Regulatory Affairs, Planning & Administration	6-17-02

FORM FDA 3397 (4/01)