

were not seen as such in the FDA assessment:

- 002_0007 has PR at last day 517
- 002_0011 has PR at last day 532
- 002_0018 has PR on day 258 and loss response day 371 (Minor, change>30%)
- 007_0019 has CR day 259, loss response day 351 (None)
- 011_0001 has PR day 183, loss day 274 (Minimal)
- 015_0002 has PR day 252, loss day 340 (None)
- 501_0025 has PR day 162, loss day 331 (Minor, change>30%)
- 501_0028 has PR day 162, loss day 419 (None)
- 502_0021 has PR day 345, loss day 518 (None)
- 503_0040 has PR day 252, loss day 336 (None)
- 503_0048 has PR day 358, loss day 449 (Minimal)
- 503_0049 has PR day 173, loss day 262 (Minimal)
- 503_0130 has PR day 85, loss day 169 (Minor, change>30%)
- 503_0132 has PR day 253, loss day 346 (None)
- 505_0004 has PR day 162, loss day 258 (None)
- 510_0005 has PR day 177, loss day 273 (None)

Three patients counted by FDA incorrectly as responders:

Patient 501_0027 is CR at baseline, should therefore not be counted as responder (counted as PR by FDA)

Patient 506_0005 never had a major response. The best response was Minimal (counted as PR by FDA)

Patient 509_0010 is CR at baseline, should therefore not be counted as responder (counted as CR by FDA)

In summary, this means:

- 1) 57 patients were counted as PR, but should be CR,
- 2) 16 additional patients should be PR
- 3) 3 patients (2 PR, 1 CR) are erroneously counted as response

by the
FDA.

Please let me know if you have any further comments or questions. I hope we can resolve these discrepancies.

Thanks again,
Bob.....

Sponsor comments

We have completed our review of the 110 data and would like to share our comments in the hopes that our numbers can agree. The largest discrepancy is in the major cytogenetic response in which we have a 60% MCR with 42% complete response. The FDA data assessment seems to show a 58% MCR with a 31% complete response.

Could you clarify if the complete response of 31% we calculated from the FDA data is actually confirmed response?

Study 110 (chronic phase CML)

Hematologic response

We accept the numbers.

Cytogenetic response

57 patients were assigned as partial response (>0%-35% Ph+) by the FDA, but had 0% Ph+ (complete cytogenetic response) at least at one assessment: See patient list below.

FDA interpretation and comments

In the Sponsor-FDA Meeting of 9/20/00 it was agreed that a cytogenetic response required a second confirmatory marrow performed at least one month after the initial marrow. Further, for CCyR designation, the confirmatory marrow had to have at least 20 metaphases. If it had fewer than 20 metaphases it could not be used as an indicator of complete cytogenetic response. In the initial study analysis FDA accepted a single cytogenetic evaluation, because of short duration follow-up, and considered it to be an unconfirmed cytogenetic response. The current submission is based on 1-2 year follow-up so that there is little justification to maintain the category of unconfirmed cytogenetic responses.

Patient	days	FDA Interpretation
001_0003	338	PR - CR is unconfirmed
002_0021	350	PR - CR is unconfirmed
003_0003	169	NR - Only day 435 data
004_0009	512	PR - CR is unconfirmed
005_0011	414	PR - CR is unconfirmed
005_0030	85	PR - CR is unconfirmed
006_0002	378	PR - CR is unconfirmed
006_0003	497	PR - CR is unconfirmed
007_0012	539	PR - CR is unconfirmed
008_0003	549	PR - CR is unconfirmed
008_0006	253	PR - CR is unconfirmed
009_0002	506	PR - CR is unconfirmed
009_0010	338	PR - CR is unconfirmed
012_0004	85,169,253	CR
014_0004	379	PR - CR is unconfirmed
015_0003	93,175,261	CR

016_0001	260,344,512	CR
016_0003	253, 505	PR - CR is unconfirmed
020_0001	176	PR - CR is unconfirmed
501_0002	170	PR - CR is unconfirmed
501_0007	170	PR - CR is unconfirmed
501_0013	169	PR - CR is unconfirmed
501_0014	338	PR - CR is unconfirmed
501_0022	337	PR - CR is unconfirmed
501_0040	337	PR - CR is unconfirmed
502_0003	421, 589	PR - CR is unconfirmed
502_0004	85,337,503	PR - CR is unconfirmed
502_0011	430	PR - CR is unconfirmed
502_0015	344, 524	PR - CR is unconfirmed
502_0024	337, 419	CR
503_0005	336	CR
503_0006	253,327,508	CR
503_0012	84	PR - CR is unconfirmed
503_0037	266	PR - CR is unconfirmed
503_0042	343	PR - CR is unconfirmed
503_0058	542	PR - CR is unconfirmed
503_0063	168,336,510	PR - CR is unconfirmed
503_0068	175,259,357	CR
503_0074	346	PR - CR is unconfirmed
503_0082	86	PR - CR is unconfirmed
503_0083	518	CR
503_0084	264,336,392	CR
503_0096	554	PR - CR is unconfirmed
503_0118	254,461,545	CR
503_0126	365	PR - CR is unconfirmed
503_0128	167	PR - CR is unconfirmed
503_0145	251, 337	CR
504_0003	337, 547	PR - CR is unconfirmed
504_0014	363	CR
505_0024	254	PR - CR is unconfirmed
509_0002	171, 424	PR - CR is unconfirmed
509_0005	247	PR - CR is unconfirmed
509_0006	74, 336	PR - CR is unconfirmed
510_0004	272,370,464	CR
511_0008	336	PR - CR is unconfirmed
512_0007	254, 431	CR
512_0010	429	PR - CR is unconfirmed

Sponsor: The following additional 16 patients are in major cytogenetic response, but were not seen as such in the FDA assessment:

FDA comment: The first 2 listed patients have an unconfirmed MCyR response and the last 14 patients had a second cytogenetic evaluation that failed to confirm a cytogenetic response. (see first FDA comment for agreed definition).

002_0007 has PR at last day 517 -unconfirmed MCyR
002_0011 has PR at last day 532 - unconfirmed MCyR
002_0018 has PR on day 258 and loss response day 371 (Minor, change>30%)
007_0019 has CR day 259, loss response day 351 (None)
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503_0049 has PR day 173, loss day 262 (Minimal)
503_0130 has PR day 85, loss day 169 (Minor, change>30%)
503_0132 has PR day 253, loss day 346 (None)
505_0004 has PR day 162, loss day 258 (None)
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Three patients counted by FDA incorrectly as responders:

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Patient 506_0005 never had a major response. The best response was Minimal (counted as PR by FDA)

Patient 509_0010 is CR at baseline, should therefore not be counted as responder (counted as CR by FDA)

FDA Comment:

Patient 501_0027 was CCyR at baseline, PcyR day 85, CCyR day 169, PcyR day 253, CCyR day 421. Therefore, evidence of Gleevec effect. Should be counted

Patient 506_0005 never had a major response. Agree

Patient 509_0010 developed and maintained a CHR while on Gleevec. Further, maintained CCyR beyond day 428. Therefore, evidence of Gleevec effect. Should be counted

Sponsor summary, this means:

- 1) 57 patients were counted as PR, but should be CR,
- 2) 16 additional patients should be PR
- 3) 3 patients (2 PR, 1 CR) are erroneously counted as response by the FDA.

Please let me know if you have any further comments or questions. I hope we can resolve these discrepancies.

FDA summary:

14 patients initially classified as PCyR are now CCyR.

One patient considered a PCyR (Patient 506_0005) is now a non-responder.

No other changes made.

FDA Final Result Study 0110

308 (58%) total cytogenetic responders

282 confirmed cytogenetic responders, 172 CCyR's and 110 PCyR's

26 unconfirmed cytogenetic responders, 6 CCyR's and 20 PCyR's

178 (33%) confirmed + unconfirmed complete cytogenetic responders (CCyR's)

172 (32%) confirmed complete cytogenetic responders (CCyR's)

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/s/

Ann Staten

1/22/02 01:25:32 PM

CSO

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: 973-781-5217

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 2

Date: December 18, 2001

Re: NDA 21-335 Gleevec

Urgent For Review Please Comment Please Reply Please Recycle

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Dear Bob,

Please refer to the sNDA for Gleevec in GIST.

I tried sending this e-mail via secure e-mail and got a notice failure.

Please call me with any questions.

Sincerely,

ann

Staten, Ann M

From: Staten, Ann M
Sent: Tuesday, December 18, 2001 9:51 AM
To: Eileen Ryan (E-mail)
Subject: Gleevec Labeling
Importance: High

Dear Bob,

We have the following questions:

In your PI table 2, we have obtained similar numbers to yours for blast crisis and chronic phase, IFN failure AEs. For accelerated phase AEs, however, we are getting higher percentages than you list. Using all grade AEs, for example, we get nausea 91%, fluid retention 89%, superficial edema 85%, diarrhea 62%, CNS hemorrhage 53%. Please check your numbers.

You also have 3 categories of muscle problems, i.e. cramps, pain, and myalgias. We think that it makes more sense to combine them in a muscle pain (myalgias, cramps) category.

thanks,
ann

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/s/

Ann Staten
12/18/01 11:21:52 AM
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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: 973-781-5217

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 1

Date: November 28, 2001

Re: NDA 21-335 Gleevec

Urgent For Review Please Comment Please Reply Please Recycle

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Dear Bob,

Please refer to the sNDA for Gleevec in GIST.

We have the following information request:

Medical:

Please submit in paper, the CRF's for the following patients:

501/007
502/025
502/026
502/110
502/125
503/018
503/036

Please call me with any questions.

Sincerely,

ann

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/s/

Ann Staten
12/4/01 09:19:33 AM
CSO

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

From: Ann Staten, Project Manager

Fax: 973-781-5217

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 2

Date: November 27, 2001

Re: NDA 21-335 Gleevec

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

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Dear Bob,

Please refer to the sNDA for Gleevec in GIST.

We have the following information requests:

Medical:

1. In the sNDA report on central pathology review, it is stated that patient 502-69 had her tumor reclassified as a non-gist tumor. The database indicates the off study date for this patient as Feb 8, 2001. Did the patient go off study prior to the reclassification or as a result of it?
2. In a response to our query, you have indicated that an additional patient was reclassified based on central review. Could you identify this patient and provide the reasons for reclassification (histologic review, c-kit status) and patient disposition?

Medical/Statistical:

1. Regarding derived data set A_TAST, please explain the difference between the date of onset of response (ONSDAT) and the interval-censored date of onset of PR (ICONSPRD)? Also, how were end dates selected for the interval-censored durations of response?
2. Why were nine patients excluded from the analysis of time to onset of response?

November 27, 2001

3. Regarding duration of response, Sponsor Figure 3-3, explain why three patients are considered at risk at 26 weeks? Is this based on the interval-censored durations of response?

Please call me with any questions.

Sincerely,

ann

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/s/

Ann Staten

11/27/01 09:23:24 AM

CSO

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Wednesday, November 07, 2001 3:37 PM
To: statena@cder.fda.gov
Subject: Answers to Questions received 11/6&7/01 via fax

Importance: High

Dear Ann -

The following information is in response to several recent queries:

1) Central review of pathology slides:
As noted in our submission, of the 124 cases reviewed, 1 was found not to be GIST. Ten additional cases were reviewed, with currently only 13 cases pending central review. Of the now total 134 reviewed, two cases (one additional case) were found not to be GIST. The issues surrounding the acquisition of the final cases include obtaining paraffin blocks from the original tumors as well as finding archived samples. We will keep you apprised of this ongoing effort, and anticipate a final report by the end of the year.

2) Discrepancy between clinical study report and TTF timelines:
The designation of two treatment failures at week 54 are based on interval censoring. Tumor assessment for these patients were scheduled according to the visit schedule in the protocol. However, the tumor assessment occurred prior to the actual scheduled tumor assessment, and the data was projected to the next visit scheduled which was at week 54 (379 days, according to the protocol).

3) Update on Phase III GIST studies:
As you know, the EORTC and the NCI are independently running two separate (yet similar) multinational studies evaluating doses of 400 mg or 800 mg daily in patients with GIST. The studies have each randomized over 700 patients. The EORTC will likely be presenting their results at ASCO 2002.

4) Method Validation: Leslie will follow-up with you with the additional copies you requested.

Thanks
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

From: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 1

Date: November 6, 2001

Re: NDA 21-335 Gleevec

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Dear Bob,

Please refer to the sNDA for Gleevec in GIST.

We have the following information request:

The report from Dr. Fletcher regarding central review of pathology is dated 8/15/01 and describes review of 124 cases. Have any of the remaining 23 cases been reviewed centrally in the interim? If so, please provide the results.

Sincerely,

ann

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/s/

Ann Staten
11/6/01 11:09:53 AM
CSO

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/Paula Rinaldi

From: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 1

Date: November 6, 2001

Re: NDA 21-335 Gleevec

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

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Dear Bob,

Please refer to the sNDA for Gleevec in GIST.

We have the following additional request:

According to the clinical study report (page 11), the first patient was enrolled on July 6, 2000. Data was obtained up to July 10, 2001 per the report. This constitutes a period of 52 weeks and 6 days. However, 2 patients are described as having time to treatment failure of 54 weeks. Please clarify this apparent discrepancy.

Sincerely,

ann

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/s/

Ann Staten

11/6/01 10:39:39 AM

CSO

Staten, Ann M

From: Staten, Ann M
Sent: Tuesday, October 30, 2001 3:29 PM
To: 'robert.miranda@pharma.novartis.com'
Cc: Staten, Ann M
Subject: RE: c-Kit Assay Kit

Dear Bob,

Here is our response to your questions:

Your proposal to use an approved reference laboratory to perform the CD117 assay as an interim measure is reasonable. The responsibility for establishing validation procedures lies with the sponsor and the selected laboratory. The Division of Oncology Drug Products will not request an inspection of such a laboratory as part of the pre-approval process for this sNDA for GIST. Specific inquiries regarding validation procedures may be addressed to CDRH.

Sincerely,

ann

-----Original Message-----

From: robert.miranda@pharma.novartis.com
[mailto:robert.miranda@pharma.novartis.com]
Sent: Tuesday, October 16, 2001 8:19 AM
To: statena@cder.fda.gov
Subject: c-Kit Assay Kit
Importance: High

FYI, we had a telcon with CDRH on Tuesday, 10/9/01, concerning the c-Kit assay. In attendance was Dr. Steven Gutman and Geretta Wood. They were very helpful and it has become apparent to us that commercialization of a kit

does not seem feasible within the sNDA timelines.

We are therefore pursuing the interim solution of a reference lab as suggested by Dr. Pazdur. CDRH informed us that FDA does not regulate reference labs. Our understanding is that they should be accredited

but this is a general assurance that covers general facilities, etc. not assay specific. The responsibility will lie with the lab and us to standardize and validate the test. We are currently working with identifying such a lab and developing a testing protocol.

FYI, some labs already exist and conduct this c-kit assay for the medical community. One such lab we are talking with is

This test

is
not FDA approved (nor required) and is for clinical purposes only. Is
something like this enough? Would some concordance testing to our
clinical
trial samples be required? If so, how many tissue samples (20 or 30)?

Given this situation, can you guide me regarding what Dr. Pazdur might
want to see if anything for a reference lab. Is proper accreditation
enough
like for the — ? Does Dr. Pazdur expect to see some data (e.g.
testing protocol, validation type report) and if so, by when (e.g. 4
months
into the sNDA review)? Would FDA also inspect such a lab as part of
the
pre-approval inspections?

Your help is greatly appreciated as we want to meet your expectations
regarding this issue.

Thanks

Bob.....

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/s/

Ann Staten

11/1/01 04:08:11 PM

CSO

Paula Rinaldi
Director
Oncology Business Unit

Novartis Pharmaceuticals
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

 **NOVARTIS**
ONCOLOGY

Tel (973) 781-7712
Fax (973) 781-6325
Email: paula.rinaldi@pharma.novartis.com

FASCIMILE

To: Ms. Ann Staten
Fax Number: 301-827-4590

Date: October 26, 2001

From: Paula E. Rinaldi (for Bob Miranda)

Reference: sNDA 21-335, Serial Number 338
Gleevec for GIST

Subject: Response to October 25, 2001 request for information

Number of Pages (including cover): 6

Dear Ann,

This is in response to your October 25, 2001 email requesting information on the CT-Scans submitted to IND [redacted] prior to the sNDA submission (SN 338) for Gleevec for GIST. You requested that we clarify which patients were responders, and explain possible discrepancies.

This information will also be submitted to the NDA.

If you have any questions, please call Paula Rinaldi (for Bob Miranda) at 973-781-7712.

Sincerely,



Paula E. Rinaldi

Distributed to:

R Dagher



Novartis Pharmaceuticals Corporation
East Hanover, NJ, USA

Clinical Development

Gleevec™ (imatinib mesylate) Capsules

GIST INDICATION

Author(s): B. Kiese, S. Dimitrijevic, S. Silberman
Document type: Response to questions from FDA re: Responders
Document status: Final
Date: 26-October-2001
Number of pages: 5

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Novartis
Follow up to FDA questions on Kit

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Page 2

Re: question from medical reviewer and request regarding responders and possible discrepancies (FDA FAX 25Oct01)

The dataset tum (and the derived dataset a_tum) refers to the "Assessment of Tumor Response" specified in the Case Report Form (CRF) for all visits in which tumor assessments were scheduled. This page was designed for the original proof-of-concept design of the study and did not collect any further details of tumor measurements.

When this study was amended and expanded into a registration study, more detailed information was requested for the tumor assessments. These are collected in the "Tumor Assessment Summary" pages, which can be found at the end of the CRF. The more extensive data from this dataset includes lesion classification, diameters, method of assessment, as well as the investigator's assessment of response. This data is contained in the datasets tma, tmc and tmd. The datasets a_tasv and a_tast are derived from the raw datasets (tma, tmc, tmd) and have been used as the basis for the study analysis.

The dataset a_tasv contains records corresponding to each patient visit and includes the response at that visit, as calculated by Novartis (based on the SWOG criteria). This response is identified by the variable called 'NOVSTA1C'.

We submitted scans for all patients who ever had any partial response (PR) listed in NOVSTA1C. Thus, this includes 89 patients. An additional patient (501.123) was also sent with NOVSTA1C='Unknown' on all post-baseline assessments due to a change in the method of tumor measurements, but who was graded as a responder by the investigator.

The dataset a_tast contains one record per patient and contains (among other variables) the best confirmed response as calculated by Novartis and identified by the variable called 'NOVSTA3C'. This best confirmed response, as stated in the protocol, was the primary endpoint of efficacy.

In summary, there are 90 patients with a PR recorded at any visit (89 with NOVSTA1C = PR, 1 with NOVSTA1C = 'Unknown'), of which 59 patients had a confirmed response (NOVSTA3C = PR) in this trial. We are attaching below the best confirmed responses for those 90 patients for whom you received scans.

If you require additional information, please do not hesitate to contact us.

APPEARS THIS WAY
ON ORIGINAL

Novartis
Follow up to FDA questions on Kit

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Page 3

**STIB2222, Best response (confirmed) as assessed by Novartis
for all patients for whom scans have been sent to FDA
10:00 Friday, October 26, 2001
(NOVSTA3C)**

	Assigned Daily Dose	Subject Identifier	Overall Best Response (Novartis Confirmed)
1.	400	0001_00012	Partial Resp.
2.	600	0001_00013	Stable Disease
3.	600	0001_00014	Partial Resp.
4.	400	0001_00037	Partial Resp.
5.	400	0001_00093	Stable Disease
6.	600	0001_00129	Stable Disease
7.	400	0001_00142	Stable Disease
8.	600	0001_00158	Stable Disease

9.	400	0501_00001	Partial Resp.
10.	600	0501_00002	Partial Resp.
11.	400	0501_00004	Partial Resp.
12.	400	0501_00006	Partial Resp.
13.	600	0501_00009	Partial Resp.
14.	400	0501_00010	Partial Resp.
15.	600	0501_00011	Stable Disease
16.	400	0501_00015	Partial Resp.
17.	600	0501_00024	Partial Resp.
18.	600	0501_00047	Partial Resp.
19.	400	0501_00048	Partial Resp.
20.	600	0501_00050	Partial Resp.
21.	600	0501_00051	Stable Disease
22.	600	0501_00053	Partial Resp.
23.	600	0501_00054	Partial Resp.
24.	400	0501_00055	Partial Resp.
25.	600	0501_00056	Partial Resp.
26.	400	0501_00060	Stable Disease
27.	400	0501_00062	Partial Resp.
28.	600	0501_00066	Stable Disease
29.	400	0501_00067	Partial Resp.
30.	600	0501_00068	Stable Disease
31.	600	0501_00072	Stable Disease
32.	400	0501_00075	Partial Resp.
33.	400	0501_00076	Partial Resp.
34.	600	0501_00078	Partial Resp.
35.	400	0501_00079	Stable Disease
36.	600	0501_00080	Partial Resp.
37.	400	0501_00084	Partial Resp.

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Follow up to FDA questions on Kit

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Page 4

38.	600	0501_00085	Partial Resp.
39.	400	0501_00087	Partial Resp.
40.	600	0501_00089	Partial Resp.
41.	400	0501_00091	Partial Resp.
42.	600	0501_00097	Partial Resp.
43.	600	0501_00099	Partial Resp.
44.	400	0501_00100	Partial Resp.
45.	600	0501_00101	Partial Resp.
46.	400	0501_00103	Stable Disease
47.	400	0501_00104	Partial Resp.
48.	600	0501_00106	Partial Resp.
49.	600	0501_00108	Stable Disease
50.	600	0501_00123	Unknown
51.	400	0501_00127	Stable Disease
52.	600	0501_00130	Stable Disease
53.	400	0501_00131	Partial Resp.
54.	600	0501_00144	Partial Resp.
55.	600	0501_00145	Stable Disease
56.	400	0501_00149	Partial Resp.
57.	400	0501_00154	Stable Disease
58.	600	0501_00156	Stable Disease
59.	400	0501_00157	Stable Disease

60.	400	0502_00025	Partial Resp.
61.	600	0502_00027	Partial Resp.
62.	600	0502_00028	Partial Resp.
63.	400	0502_00029	Stable Disease
64.	400	0502_00035	Partial Resp.
65.	600	0502_00042	Partial Resp.
66.	400	0502_00043	Stable Disease
67.	400	0502_00059	Partial Resp.
68.	400	0502_00064	Stable Disease
69.	600	0502_00073	Partial Resp.
70.	600	0502_00090	Partial Resp.
71.	400	0502_00107	Stable Disease
72.	600	0502_00109	Partial Resp.
73.	400	0502_00133	Partial Resp.
74.	600	0502_00150	Stable Disease

75.	600	0503_00016	Not Evaluable
76.	400	0503_00017	Stable Disease
77.	600	0503_00021	Partial Resp.
78.	400	0503_00022	Partial Resp.
79.	600	0503_00031	Partial Resp.
80.	600	0503_00041	Partial Resp.

Novartis
Follow up to FDA questions on Kit

Confidential

Page 5

81.	600	0503_00044	Partial Resp.
82.	400	0503_00058	Partial Resp.
83.	600	0503_00065	Partial Resp.
84.	600	0503_00071	Partial Resp.
85.	400	0503_00096	Stable Disease
86.	600	0503_00114	Partial Resp.
87.	400	0503_00119	Partial Resp.
88.	400	0503_00124	Progressive Dis.
89.	600	0503_00135	Partial Resp.
90.	400	0503_00138	Stable Disease

APPEARS THIS WAY
ON ORIGINAL

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: *Paula R.* From: Ann Staten, Project Manager

Fax: *973-781-6325* Fax: 301-827-4590

Phone: Phone: 301-594-5770

Pages: *2* Date: *10/25/01*

Re: *See attached*

Urgent For Review Please Comment Please Reply Please Recycle

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● Comments:

Staten, Ann M

From: Staten, Ann M
Sent: Thursday, October 25, 2001 11:05 AM
: 'eileen.ryan@pharma.novartis.com'
Subject: Secure E-mail for Paula R. (re: Gleevec - GIST)

Importance: High

Dear Paula,

Here is a question from our review of the CT-Scans submitted to the IND
prior to the sNDA submission (serial no. 338)Gleevec for GIST.

Medical reviewer request:

You are claiming a response rate of 40.1% based on a confirmed response in 59 patients. However, in your submitted dataset A.TUM, we find that 83 patients had a PR on at least one evaluation and 63 patients had a PR on more than one evaluation. Furthermore, you have submitted scans on 90 patients designated as 'responders' in the accompanying text submission. Please clarify these apparent discrepancies and submit the designation of best response for the 90 patients for whom scans were submitted.

Please call me upon receipt to clarify any questions.

thanks,
ann

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 for Ellen Cutler

From: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 1

Date: April 4, 2001

Re: IND CGP 57148B (STI571)- GIST indication- serial no 185

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Dear Bob,

Please refer to our fax dated 3-21-01 which provided the responses to your questions for the GIST indication (background package dated 3-2-01; N185).

The following are additional comments from the statistical review:

Statistical Issues and Comments:

1. You should set up a criteria for the primary efficacy endpoint (criteria for the lower limit of an exact two-sided 95% confidence interval for the response rate).
2. You should submit analyses based on both the ITT population and the Efficacy Analyzable population. We will consider the ITT analyses as primary.

Sincerely,

Ann

/s/

Ann Staten

4/11/01 03:41:21 PM

CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development (HP-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

November 1, 2001

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

Attention: Robert A. Miranda
Associate Director, Drug Regulatory Affairs

Dear Mr. Miranda:

Reference is made to your request for orphan-drug designation dated August 9, 2001, of imatinib for the treatment of gastrointestinal stromal tumors (designation request # 01-1492), submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (21 USC 360bb).

We have completed the review of this request and have determined that imatinib qualifies for orphan designation for the treatment of gastrointestinal stromal tumors. Please note that it is imatinib and not its formulation that has received orphan designation. You have notified us that you are currently developing imatinib under the trade name Gleevec™.

Please be advised that if imatinib is approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FDCA (21 U.S.C. 360cc). Therefore, prior to final marketing approval, sponsors of designated orphan drugs are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of imatinib as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved (21 CFR 316.30). If you need further assistance in the development of your product for marketing, please feel free to contact Jack McCormick, MD, in our office at (301) 827-3666.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan-drug designation.

Sincerely yours,

/s/
Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080



Tel 973 781 7500
Fax 973 781 6325

Facsimile transmittal

To: Ann Staten Fax: 301-827-4590

Co: _____

From: Robert Miranda Date: NOVEMBER 2-2001

Re: _____ Pages: 3 pages including cover

Urgent For Review As Requested Please Reply



**MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS**

DATE: December 12, 2001 (8:30am-9am)

SUBJECT: NDA 21-335 Gleevec (imatinib mesylate)

Discussion:

Dr. Nerestone was consulted regarding the supplemental application for Gleevec in gastrointestinal stromal tumors (GIST). Dr. Nerestone concurred with the Division's decision to approve this application under the subpart H accelerated approval condition with the phase 4 commitments to include submission of more mature data for response, duration of response, and survival from study B2222, submission of data from the ongoing NCI and EORTC trials comparing 400 mg daily to 800 mg daily, and the development of a commercial c-Kit assay.

Ann Staten, RD
Regulatory Health Project Manager

Ramzi Dagher, MD
Medical Reviewer

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this page is the manifestation of the electronic signature.**

/s/

Ann Staten
12/19/01 02:47:01 PM
CSO

Ramzi Dagher
12/19/01 03:26:56 PM
MEDICAL OFFICER

**MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS**

DATE: December 12, 2001 (9am-9:30am)

SUBJECT: NDA 21-335 Gleevec (imatinib mesylate)

Discussion:

Dr. Redman was consulted regarding the supplemental application for Gleevec in gastrointestinal stromal tumors (GIST). Dr. Redman concurred with the Division's decision to approve this application under the subpart H accelerated approval condition with the phase 4 commitments to include submission of more mature data for response, duration of response, and survival from study B2222, submission of data from the ongoing NCI and EORTC trials comparing 400 mg daily to 800 mg daily, and the development of a commercial c-Kit assay.

Ann Staten, RD
Regulatory Health Project Manager

Ramzi Dagher, MD
Medical Reviewer

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/s/

Ann Staten
12/19/01 02:45:26 PM
CSO

Ramzi Dagher
12/19/01 03:21:19 PM
MEDICAL OFFICER

INTERNAL MEETING MINUTES

MEETING DATE: July 12, 2001 **TIME:** 2: 00 pm **LOCATION:** Conference Room B

IND/NDA **IND** **Meeting Request Submission Date:** June 12, 2001 (N249)
Briefing Document Submission Date: June 28, 2001 (N262)

DRUG: Gleevec (imatinib mesylate)

SPONSOR/APPLICANT: Novartis

TYPE of MEETING:

1. pre-sNDA
2. **Proposed Indication:** Patients with unresectable or metastatic gastrointestinal stromal tumors (GIST).

FDA PARTICIPANTS:

Richard Pazdur, M.D. Division Director
Grant Williams, M.D., Medical Team Leader
Martin Cohen, M.D., Medical Reviewer
Atik Rahman, Ph.D., Team Leader, Clin. Pharm.
John Leighton, Ph.D., Pharm/Tox Team Leader
Kimberly Benson, Ph.D., Pharm/Tox Reviewer

MEETING OBJECTIVES:

To discuss the registration plan for the indication GIST.

BACKGROUND: Following the internal pre-meeting on July 12, 2001, FDA's responses were sent to the sponsor on July 12, 2001. The sponsor felt that the Agency responses were clear and the sponsor cancelled the meeting.

DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Attached is the E-mail dated July 12, 2001.

Ann Staten Date
Project Manager
Minutes preparer

Electronic Mail Message

Date: 7/12/01 3:29:35 PM
From: Ann Staten (STATENA)
To: eileen.ryan (eileen.ryan@pharma.novartis.com)
Subject: IND [redacted] pre-sNDA meeting

Dear Bob,

Attached are the FDA answers to your questions. As we discussed earlier, you have the option of canceling our meeting of July 17, 2001 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.

Thanks,

ann

IND Gleevec

Pre-sNDA meeting for 7-17-01

Chemistry, Manufacturing and Controls

1. The treatment of GIST will use the same drug product as currently approved for CML, therefore no CMC section is planned for this SNDA. Do you agree with this approach?

FDA Response: The approach is adequate.

Preclinical

2. Our original NDA for CML contains all of the pertinent preclinical safety data for Gleevec. Since the filing of this original NDA, some additional reports have been issued in the Preclinical Drug Metabolism and Pharmacokinetics Department.

These new reports are listed in section 4.1, and are not planned to be included into the SNDA for the GIST indication. They are available on request and will be included in the next IND annual report.

No preclinical safety data is therefore planned for this SNDA. Do you agree with this approach?

FDA Response:

We concur with this approach, provided that no change in the label is intended for any of the pharmacology/toxicology sections, including but not limited to, safety toxicology and mechanism of action.

3. Our original NDA for CML contained a summary discussion and list of pertinent preclinical pharmacology studies. The preclinical pharmacology studies listed in Section 4.2 were done to evaluate the potential antitumor effects in solid tumor models and were not included in the CML NDA.

Although these studies were done to evaluate the potential antitumor effects in solid tumors they are not specific for GIST and are not of direct relevance to this indication. As such we propose not to include these internal pharmacology studies in this SNDA. Do you agree with this approach?

FDA Response: See response to question #2

Two reports were discussed in the original NDA for CML. (Ref 1,2 and Section 4.2) which support the GIST indication because they show inhibition of the Kit tyrosine

kinase mediated signal transduction. Furthermore, a manuscript describing the inhibition of *c-kit* oncoprotein and proliferation of GIST cells by Gleevec (Section 3.2) has been accepted for publication. (Ref 3)

In summary, no preclinical data is planned for this SNDA. Do you agree with this approach?

FDA Response: See response to question #2

Clinical Pharmacology

4. Our original NDA for CML contains all the pertinent clinical pharmacology data for Gleevec. The only pharmacokinetic data planned for this SNDA will contain pharmacokinetic data from the pivotal GIST trial. As such, no Item 6 (Human PK and Bioavailability Section) and Clinical Pharmacology Studies subsection of Item 8 is planned for this SNDA. A comparison of PK in GIST patients with CML patients will be provided in Item 3 (PK Summary). In addition, PK parameters and PK/PD analysis in GIST patients will be included in the clinical trial report for Study B2222 (see analysis plan in RAMP document-Attachment 3). Do you agree with this approach?

FDA Response: No.

- Please provide pharmacokinetic data and data analysis from pivotal GIST trial in Section 6 of the sNDA.
- You should make a pharmacokinetic comparison of data from GIST patients and CML patients and explore PK/PD relationship from the GIST trial. Please provide these analysis in item 6 of the sNDA.
- Please provide all relevant information in this section, including all raw data, detailed analysis and assay description and validations.
- Please modify the composition and the table of content of this sNDA accordingly.

Clinical and Statistical

(Data presentation in pivotal trial)

Novartis has outlined our intended presentation of the efficacy and safety data for the key efficacy trial B2222 in Section 4.3 and Attachments 3-6

5. We have described the rationale for targeting the lower level of the confidence interval (95%, two-sided, Pearson-Clopper limits) of at least 10% response in the TRT (treated) population in Section 4.3.1, Statistical Analysis Considerations. For 148 patients, this coincides with an observed response rate of 15.5 %. Does the Division concur with using this 10% lower-limit of confidence-interval?

FDA Response: This is a review issue. Under accelerated approval regulations, FDA must find that the results demonstrate an improvement over available therapy and that they are reasonably likely to predict clinical benefit. These judgements may involve not only an assessment of response rate but also other clinical details, including response duration.

6. Does the Division concur with the proposals for the efficacy analysis for study B2222, including the definitions of analysis populations: TRT (treated) and EA (efficacy analyzable) as defined in Section 4.3.2?

FDA Response: The TRT population is acceptable. The EA population should consist of patients who did not meet eligibility/ineligibility criteria. The fact that they did or did not receive 21 days of treatment is not relevant. In analyzing efficacy results emphasis will be directed toward the TRT population.

7. Does the Division concur with the proposals for the safety analysis for study B2222 (Section 4.3.3)?

FDA Response: Yes.

(Composition / Presentation of Integrated Summaries)

8. **Integrated efficacy summary (ISE):** The ISE will contain the summary of efficacy data from a single study (B2222) (Section 4.4). The presentation of efficacy data from study B2222 is outlined in Attachments 3-5 and is in compliance with comments contained in the FDA EOP2 fax dated 21 March 2001. Do you agree with this approach?

FDA Response: It is agreed that efficacy results from study B2222 should be compared to historical data. That historical data must consist of patients with a histologic diagnosis of GIST whose tumors express CD 117 on the cell surface.

9. **Integrated Safety Summary (ISS):** The ISS will consist of full safety data for patients on study B2222 and listing of reported SAEs for other ongoing solid tumor studies through a cutoff date of 30 April 2001 as agreed in the FDA EOP2 fax dated 21 March 2001 (Section 4.5). Events occurring after this date will be included in the 120-day safety update. Relevant safety experiences in CML will be referenced. Do you concur with this approach?

FDA Response: Yes

10. Are the ISS tables appropriately designed so as to facilitate your review? (Sections 4.4 and 4.5 and Attachments 3-5)

FDA Response: Yes

11. The composition of Section 10 (statistical section) of the SNDA is largely a duplication of information contained in Section 8 (clinical section) of the SNDA. We propose to submit in Section 10 identical copies of the relevant SNDA 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 (CRTs)

12. Do you concur with our presentation of CRTs as described in Section 4.6 to satisfy the requirements of 21 CFR 314.50(f)(1)?

FDA Response: Yes

Narratives and Case Report Forms (CRFs)

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

FDA Response: All SAE's regardless of trial drug relationship, rather than specific SAE's regardless of trial drug relationship, should be submitted.

Electronic Submission

14. Does the Division concur with our proposed electronic submission of documentation as outlined in Section 4.8? Are there any specific requests/requirements that should be considered to facilitate review of this application?

FDA Response: Please provide all dates in date/time format, i.e. 1/11/01.

15. 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

SNDA Table of Contents

16. The proposed table of contents for this SNDA is provided as Attachment 7. Is this acceptable?

FDA Response: Yes

Regulatory Considerations

Financial Disclosure

17. We propose to submit the appropriate Financial Disclosure certification in accordance with the Final Rule published in the 31 December 1998 Federal Register for all investigators who enrolled patients in Study B2222 as of 2 February 1999. These studies are the basis for establishing the safety and efficacy of Gleevec for the proposed indication. Is this acceptable?

FDA Response: Yes

Pediatric

18. GIST is rare in children and we request a full waiver for the provision of pediatric data for this indication. Do you agree that a pediatric waiver is appropriate for Gleevec in this indication?

FDA Response: Yes

Priority Review

19. We believe that Gleevec promises to provide a meaningful therapeutic benefit to patients (e.g. ability to treat patients for whom no reasonable alternative exists or patients who are unresponsive to, or intolerant of, available therapy) and should qualify for a priority review in that it demonstrates safety and efficacy in addressing an unmet medical need. Does the Division agree that the demonstration of an outstanding risk-benefit assessment in the proposed patient population would support a priority review?

FDA Response: This is a review issue

Additional Medical Comments:

1. Please provide the x-rays for all responders (baseline and best response).
2. Please clarify the status of the c-kit assay.
 - Is it commercially available?
 - Does it correspond with the c-kit assay used in your study?
 - Is it quantitative?

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. Pediatric Exclusivity

Under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension if Gleevec 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 Request (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*" at Drug Information Branch (301) 827-4573 or <http://www.fda.gov/cder/guidance/index.htm>. You should also refer to our division's specific guidance on pediatric oncology Written Requests which is at <http://www.fda.gov/cder/guidance/3756dft.htm>.

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/s/

Ann Staten

11/21/01 01:33:37 PM

Previously checked into DFS on 8-2-01 but removed and
replaced due to formatting errors.

INTERNAL MEETING MINUTES

MEETING DATE: March 20, 2001 **TIME:** 2:30pm **LOCATION:** Conference Room B

IND/NDA IND [redacted] Meeting Request Submission Date: December 21, 2000 (N146)
Briefing Document Submission Date: March 2, 2001 (N185)

DRUG: STI571

SPONSOR/APPLICANT: Novartis

TYPE of MEETING:

1. EOP2
2. **Proposed Indication:** Patients with unresectable or metastatic malignant gastrointestinal stromal tumors (GIST).

FDA PARTICIPANTS:

Robert Temple, M.D., Director, Office of Drug Evaluation I
Richard Pazdur, M.D. Division Director
Grant Williams, M.D., Medical Team Leader
Martin Cohen, M.D., Medical Reviewer
Gang Chen, Ph.D., Team Leader, Statistics
Mark Rothmann, Ph.D., Statistics
Atiqur Rahman, Ph.D., Team Leader, Clinical Pharmacology and Biopharmaceutics
Lydia Kieffer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Ann Staten, R.D., Regulatory Project Manager

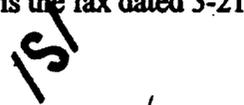
MEETING OBJECTIVES:

1. To discuss the adequacy of Novartis's development plan for GIST.

BACKGROUND: Following the internal pre-meeting on 3-20-01, FDA's responses were faxed to the sponsor on 3-21-01. The sponsor felt that the Agency responses were clear and the sponsor cancelled the 3-27-01 meeting.

DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Attached is the fax dated 3-21-01.



Ann Staten Date
Project Manager
Minutes preparer

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To: Ellen Cutler

From: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 4

Date: March 21, 2001

Re: IND [redacted] CGP 57148B (STI571) – EOP2 meeting for GIST – serial no 185

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Ellen,

Attached are the FDA answers to your questions. You have the option of canceling our meeting of March 27, 2001 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.

Sincerely,

Ann

**Glivec (imatinib mesylate)
Meeting Questions for 3/27/01 meeting**

1. **The target patient population is described in section 3. These patients have unresectable or metastatic malignant GIST, with their histological tissue diagnosis confirmed on the basis of expression of CD117 in tumor tissue samples. Is the population adequately defined both histopathologically and clinically?**

FDA Response:

Your study population is defined on the basis of light microscopy and the expression of CD117 in tumor tissue samples. In order for the FDA to evaluate STI571 efficacy in this patient population it will be necessary for the sponsor to provide a literature review of chemotherapy results in similarly defined patients. While older literature suggests that GIST response rates are low the current GIST population might differ substantially from populations included into those studies.

2. **We plan to analyze time to treatment failure based on the definitions and criteria provided in section 3. Is this end point and the analysis proposed to register Glivec in this indication acceptable to the division?**

FDA Response: No

Neither TTF nor TTP provide useful information in phase II studies. Further, TTF is not a pure efficacy measure. The preferred endpoints are response rate and response duration. If clinical benefit parameters were evaluated these results should be provided.

3. **Will an overall response rate of > 20% and a time to treatment failure at least 2 fold greater than that of the historical control group provide sufficient evidence of activity to support this registration?**

FDA Response:

This is a review issue. (see response to question 1)

4. **The original study design was a proof-of-concept trial and had response rate as the primary efficacy objective and time to tumor progression (progression free survival) as a secondary efficacy endpoint. Is it necessary to amend the protocol to revise the primary efficacy endpoint as time to treatment failure to be in accord with this submission?**

FDA Response: No

See response to question 2

5. Is the proposed historical control described in section 3 adequate as a basis upon which to compare the efficacy of Glivec?

FDA Response: Not necessarily

The appropriate control group should have a light microscopic appearance compatible with GIST and should be CD117 positive.

6. Can the data with ¹⁸FDG-PET scanning be considered as additional supportive evidence of pharmacodynamic activity of Glivec and evaluated as an early indication of response in these patients?

FDA Response:

The ¹⁸FDG-PET scanning data will be interesting and may provide insights into how to use this study in the future but it cannot replace traditional radiologic tumor evaluation methods.

7. We propose to provide full safety data for patients on this study. Serious adverse events for ongoing solid tumor studies will be provided through a cutoff date of 30 April 2001. Events occurring after this date will be included in the 120 day safety update.

CRF and narratives will be provided. These will include:

- Deaths other than due to disease progression
- Patients who discontinued for treatment-related serious adverse events
- SAEs:
 - All trial drug related
 - Specific SAEs regardless of trial drug relationship
 - ◆ Rash
 - ◆ Liver enzyme abnormalities
 - ◆ Fluid retention and edema
 - ◆ Renal toxicity
 - ◆ GI tract hemorrhage
 - ◆ Subdural or cerebral hematomas or hemorrhages

In addition, we will refer to the relevant safety information submitted in the CML dossier (summarized in Appendix 3) through the 120 day safety update on the 1000 patients in the

CML phase 2 programs, including serious adverse events in the expanded access programs.

Is this proposal for the reporting of safety data acceptable to the division in support of this registration?

FDA Response: Yes

8. Is the information that will be provided in this supplemental NDA sufficient to gain approval of Glivec for the treatment of unresectable or metastatic malignant GIST?

FDA Response: This is a review issue.

If the response rate is clearly higher than that which can be achieved with available therapy and if the response rate and response duration appear reasonably likely to predict clinical benefit, the FDA may consider approval under subpart H.

Additional Clinical Pharmacology and Biopharmaceutics Comments:

1. We recommend that you evaluate PK/PD assessment in Study B2222. PK may be correlated with efficacy measures such as tumor response, time to disease progression, measurement of indices of cellular proliferation and immunohistochemical evaluation of expression and phosphorylation status of Kit, and other relevant tyrosine kinase molecules or downstream effector molecules. PK/PD correlates with safety may include rash, liver enzyme abnormalities including bilirubin status, renal toxicity, GI tract hemorrhage, and subdural or cerebral hematomas or hemorrhages.
2. Patients on warfarin therapy were either excluded from study or switched to low molecular weight heparin. Do you intend to perform a formal drug interaction study to better assess how to dose patients on warfarin therapy and/or Glivec therapy?
3. Patients on acetaminophen therapy are to be followed closely while on study due to potential for a drug interaction. Do you intend to perform a formal drug interaction study to better assess the potential risks in acetaminophen co-administration?
4. Semen analysis is being performed for sperm density, viability, motility, and morphology in male patients whenever possible. Are you also planning to perform a PK analysis to assess any correlations between PK and the above covariates?

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/s/

Ann Staten

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to formatting problems