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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-335/S-001

Medical Review(s)

Clinical Review Cover Sheet

Application #	**21-335/S01**
Drug Name	**Gleevec™ (imatinib mesylate)**
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Documents reviewed	**M16.1-M16.9**

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Clinical Review for NDA 21-335S01

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA recommends approval of Gleevec™ (imatinib mesylate capsule) for the treatment of patients with metastatic or unresectable malignant gastrointestinal stromal tumors (GIST) under subpart H (accelerated approval) of the NDA regulations. Accelerated approval under subpart H applies to drugs for serious or life-threatening diseases. For indications where the new drug appears to provide benefit over available therapy, FDA may grant accelerated approval based on a surrogate endpoint that is reasonably likely to predict clinical benefit. After approval, the sponsor is required to perform a post-marketing study to demonstrate that treatment is associated with clinical benefit. If the studies fail to demonstrate clinical benefit or if the sponsor does not show due diligence, the drug may be removed from the market.

The assessment of benefit in this application is based on the surrogate endpoint of objective response. The efficacy results for this surrogate endpoint are summarized in section II of this document. For the treatment indication of metastatic or unresectable malignant GIST, the DODP has determined that the effect of imatinib treatment measured by this surrogate endpoint is better than would be expected with available therapy. For patients with unresectable or metastatic disease, no effective therapy exists.

With regard to risks associated with imatinib therapy, the FDA's previous review of imatinib for the treatment indication of chronic myelogenous leukemia identified a number of concerns. The review of the new database of patients with recurrent or metastatic GIST has allowed identification of the following issues, most of which are common to those noted in the prior CML review:

Nausea: As in patients with CML, nausea is encountered in more than half of all patients with GIST receiving imatinib.

Edema and fluid retention : As in patients with CML, most patients with GIST receiving imatinib develop superficial edema and some develop more serious, but rarely life-threatening, fluid retention.

Cytopenias : Imatinib was noted in the prior review to decrease the number of white blood cells and platelets in patients with CML, increasing the risk of infection and risk of bleeding. In

patients with GIST, lowering of white blood cells and platelets occurs less commonly, possibly due to the lack of any underlying bone marrow pathology in most patients.

Hemorrhage : Bleeding was observed in nearly 20% of GIST patients treated with imatinib. In seven patients, imatinib was associated with bleeding into the tumor or gastrointestinal tract. One patient with a cerebrovascular accident was reported.

Liver toxicity : Elevations in liver transaminases have been noted in patients with CML as well as patients with GIST. Monitoring is especially important in patients with GIST, since many of these patients also have metastatic disease in the liver.

Drug-drug interactions : Significant drug-drug interactions have been previously observed with imatinib. Imatinib is metabolized by, and also inhibits, hepatic P450 isoenzyme CYP3A4. Human liver microsome studies have demonstrated that imatinib is a competitive inhibitor of CYP2C9 and CYP2D6.

In the GIST clinical trial, patients were randomized to a dose of 400 mg/day or 600 mg/day. However, the study was not powered to detect a statistically significant difference in objective response rates between the two dosing regimens and no such difference was observed. Small differences in the safety profile between the two dose levels studied did not permit a conclusion that the risk/benefit ratio of one dose level was superior to the other.

It is the clinical judgement of the FDA clinical review team that the potential benefits outweigh the risks associated with imatinib treatment of advanced GIST using a dose of 400 mg or 600 mg daily. However, it should be emphasized that the duration of followup in patients with GIST treated with imatinib is limited at this point. Therefore, new safety data from ongoing trials should be evaluated promptly by Novartis and new information communicated to physicians and patients.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

1. Binding phase 4 commitments under accelerated approval

The sponsor will be required to :

A. Complete the follow-up of sNDA trial B2222 and submit mature response rate, response duration, and survival data. The suggested timelines for these submissions are December 31 of 2002 for response and response duration, and after either 70% of events have occurred or 5 years of follow-up for survival analysis (March 31, 2007).

B. Submit an updated report of the central pathology review for sNDA trial B2222 when review of the 13 pending cases is complete (June 2002).

C. Submit data from the two ongoing multicenter trials of imatinib that are testing 400 mg/day versus 800 mg/day in patients with GIST (EORTC and NCI sponsored trials). Response rate, duration of response, safety and survival data should be submitted. The data should be submitted in a timeline consistent with the statistical analysis plan of each respective protocol (estimated June 2003).

D. Submit clinical and PK data for the EORTC phase 1 study of imatinib in patients with GIST and other soft-tissue sarcomas (Submission July 31, 2002).

E. Assure availability of a validated test kit for detection of CD117 tumor expression by immunohistochemistry. Timelines are as follows :
Pre-Market Application (PMA) filing by 3rd party planned by December 31, 2002

2. Other phase 4 commitments

A. Provide a plan for investigating the incidence and etiology of GI/tumor hemorrhage associated with imatinib therapy (Submission : July 31, 2002)

B. Investigate and submit data regarding :
1) correlation of c-kit tumor mutation status with clinical outcome
2) tumor c-kit phosphorylation status at baseline and post-exposure to imatinib
3) correlation between serum VEGF levels and response
(Submission : December 31, 2002)

C. Implement a physician and patient education program for GIST regarding the use of concomitant medications with imatinib within 2 months of the date of this letter.

Pediatric studies

D. Submit the final study report for the phase 1 trial of imatinib being conducted in children with relapsed/refractory Ph+ leukemias (Protocol 103 being conducted by the Children's Oncology Group) as part of the phase 4 commitments for the imatinib approval for CML.

E. Complete a phase 2 efficacy study in an appropriate pediatric population as previously agreed as part of the phase 4 commitments for the imatinib approval for CML.

Pharmacokinetics and drug interactions

F. Complete the following ongoing studies being conducted as part of the phase 4 commitments for the imatinib approval for CML:

Drug-drug interaction studies with acetaminophen, dextromethorphan (CYP2D6 substrate), and rifampin (CYP3A4 inducer)

PK study in patients with liver impairment

G. Submit the PK/PD data from the comparison of 400 mg/day versus 800 mg/day in GIST patients in the two ongoing multicenter trials of imatinib (EORTC and NCI sponsored trials) (Submission : June 30, 2003).

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Imatinib mesylate (Gleevec™, STI571) is an orally administered inhibitor of a number of tyrosine kinases. It is known to inhibit the Bcr-Abl kinase, an aberrant kinase produced in CML as a result of a translocation known as the Philadelphia chromosome. Imatinib also inhibits the c-kit receptor tyrosine kinase, which is found on tumor cells of over 95% of patients with malignant GIST. Laboratory data suggest that imatinib also inhibits another tyrosine kinase known as the platelet-derived growth factor receptor (PDGFR).

The treatment options for patients with malignant GIST are limited. Chemotherapy regimens result in a tumor response in no more than 5% of patients. Radiation therapy has not been shown to be of any benefit. Surgical resection is an option, but there is a significant risk of relapse even after complete resection. For patients with unresectable disease, no alternative therapy exists. For patients with metastatic disease, surgery offers palliation at best.

Novartis has submitted one phase 2, open-label, study of imatinib mesylate in 147 patients with metastatic and/or recurrent malignant GIST : Study B2222. Patients in this study were randomized to doses of 400 mg vs 600 mg daily.

B. Efficacy

The DODP is recommending accelerated approval of this sNDA based on the surrogate endpoint of objective response. At the time of the cut-off date for the study report, an overall objective response rate for both dose levels combined of 38% was documented (56/147 patients). The response rate was 33% (24/73) in the 400 mg dose group and 43% (32/74) in the 600 mg dose group.Because of short followup, the median duration of response cannot be determined, and the final response rate could possibly be higher, as there were patients with unconfirmed partial responses and patients with stable disease who were still receiving drug at the cut-off date. As discussed elsewhere, there is no available therapy likely to yield a comparable objective tumor response in this population.

C. Safety

1. Adequacy of safety testing

The following table summarizes the exposure to imatinib in the sNDA GIST database by the FDA's assessment.

Initial dose (mg/day) Duration of exposure	400 (N=73)	600 (N=74)	All doses (N=147)
≤ 6 months	58 (79%)	54 (73%)	112 (76%)
> 6 - ≤ 12 months	15 (21%)	20 (27%)	35 (24%)
Total	73 (100%)	74 (100%)	147 (100%)

At the last date of assessment prior to the study report cut-off, the majority of patients on study had a duration of exposure of ≤ 6 months. In addition to the 147 patients with GIST treated with imatinib, FDA has previously reviewed safety data from approximately 1,100 patients treated with imatinib at similar doses and dosing schedules for chronic myelogenous leukemia (CML) in one phase 1 trial and three phase 2 trials of imatinib in accelerated phase, chronic phase, and blast crisis CML.

2. Serious side effects

Serious adverse events (SAE's) were reported in 29% of patients in the safety database. As observed in the CML database, grade ¾ fluid retention, edema, diarrhea, vomiting, abdominal pain and hepatotoxicity were noted in patients with GIST but in a relatively low percentage of patients for each unique AE. Hemorrhage at the tumor site and at extratumoral sites was observed in some patients with GIST.

a. Hemorrhage

Bleeding was noted in 27 (18%) patients. Of these, 7 had hemorrhages into the gastrointestinal tract or sites of tumor involvement, and 1 patient had a cerebral hemorrhage. Bleeding did not correlate with low platelet count, large tumor burden, or duration of treatment. It is hypothesized that some hemorrhages may have been due to the rupture of tumor masses within the wall of the

stomach or small intestine. Sixteen of these 25 patients had less severe bleeding episodes such as subconjunctival hemorrhage or guiac positive stool.

b. Fluid retention and edema

Extremity and facial edema occurred commonly in patients with GIST, reported in 36.1% and 59.2% of all patients respectively. Internal fluid retention such as ascites or pleural effusion was uncommon, reported in 2% of all patients. Grade ¾ edema was also uncommon, reported in 5% of all patients in the study. There was no clear relationship between dose and severity or nature of edema.

c. Hepatotoxicity

Elevations in SGOT or SGPT were noted in 49.7% and 34% of all patients respectively. Grade ¾ elevations in bilirubin occurred in 4 (2.7%) patients. All 4 had hepatic metastases as did all 5 patients with grade ¾ elevations in SGPT and all 4 patients with grade ¾ elevations in SGOT.

d. Hematologic abnormalities

Although anemia, neutropenia, and thrombocytopenia occurred commonly in patients with GIST treated with imatinib (94.6%, 42.9% and 23.1% respectively), grade ¾ hematologic abnormalities were rarely seen (anemia 4.8%, neutropenia 7.5%, thrombocytopenia 1%). The relatively decreased severity of hematologic toxicity in GIST patients compared to those with CML is possibly related to the lack of underlying bone marrow pathology in most GIST patients.

e. Gastrointestinal (GI) adverse events (AE's)

GI system events of nausea and diarrhea were the most frequently encountered (55 % and 58 % of patients, respectively). Diarrhea was second to fluid retention as the most common adverse event observed in the study.

3. Drug-drug interactions

There is a significant increase in exposure to imatinib in healthy subjects when the drug is co-administered with ketoconazole , a CYP3A4 inhibitor. Imatinib also increases the mean Cmax and AUC of simvastatin, a CYP3A4 substrate. Furthermore, a patient on therapy with phenytoin (a CYP3A4 inducer) given 350 mg daily dose of Gleevec™ had an AUC_{0-24} about 1/5 of the typical AUC_{0-24}. Human liver microsome studies have also demonstrated that imatinib is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5.

Cautions relevant to drug interactions already outlined in the label for imatinib include the following:

a. Caution when administering the drug with inhibitors of the CYP3A4 family (i.e. ketoconazole) as this may decrease imatinib metabolism and increase its concentrations.
b. Co-medications that induce CYP3A4 such as rifampin or phenobarbital may reduce exposure to imatinib.
c. Drugs that are CYP3A4 substrates may have their plasma concentrations increased by imatinib.
d. Because warfarin is metabolized by CYP2C9, patients who require anticoagulation should receive low-molecular weight or standard heparin.

4. Warnings

Aside from warnings already present in the label, additional information was added to the precautions section of the label based on the hemorrhagic events observed in the GIST trial :

a. In the GIST clinical trial, seven patients (5%), four in the 600 mg dose group and three in the 400 mg dose group had a total of eight events of CTC grade ¾ gastrointestinal (GI) bleeds (3 patients), intratumoral bleeds (3 patients), or both (1 patient). Gastrointestinal tumor sites may have been the source of GI bleeds.

5. Unresolved safey issues

The underlying mechanism for the development of edema has not been identified. Management has included diuretics or steroids in some patients, but an optimal medical intervention has not been found.

The etiology of the bleeding observed into the GI tract or intratumoral sites has not been established. These episodes were not correlated with thrombocytopenia or tumor bulk in GIST patients.

D. Dosing

In patients with CML, the recommended dosage is 400 mg/day for patients in chronic phase and 600 mg/day for patients in accelerated phase or blast crisis.

A dose of 400 mg daily or 600 mg daily will be recommended in GIST patients. In the GIST clinical trial, patients were randomized to a dose of 400 mg/day or 600 mg/day. However, the study was not powered to detect a statistically significant difference in objective response rates between the two dosing regimens and no such difference was observed. Small differences in the safety profile between the two dose levels studied did not permit a conclusion that the risk/benefit ratio of a dose level was superior to the other.

The GIST study allowed patients with progressive disease on a dose of 400 mg daily to have a dose increase to 600 mg daily. Of 12 patients who were randomized to 400 mg daily and had dose increases to 600 mg daily for progressive disease, none had a subsequent confirmed assessment of a complete or partial response. The relevance of stable disease reported in two patients is unclear, particularly with the limited followup in the study.

The EORTC phase 1 study of imatinib in patients with GIST and soft tissue sarcomas consisted of dose escalations up to a dose of 500 mg BID (1000 mg/day). At this dose level, 3 patients had grade 3 nausea/vomiting, 1 had grade 3 edema, and one had grade 3 dyspnea. Dosing at 400 mg BID (800 mg/day) was well tolerated with dose limiting neutropenia noted in only one patient. **Further information regarding efficacy and safety of dosing at 800 mg/day in GIST patients will be available from the ongoing NCI and** EORTC sponsored trials of 400 mg/day vs 800 mg/day of imatinib.

E. Special Populations

1. Pediatrics

There are no data in pediatric patients. A phase 1 study in pediatric patients with Philadelphia chromosome positive leukemias is ongoing. There is a prior commitment from the sponsor to conduct a phase 2 study in an appropriate pediatric population.

2. Elderly

In the GIST study, 29% of patients were older than 60 years and 10% were older than 70 years. No obvious differences in the safety or efficacy profiles were noted in patients older than 65 years as compared to younger patients, but the small patient numbers makes drawing definitive conclusions impossible.

3. Renal or Hepatic Impairment

No studies in renal or hepatic impaired patients have been completed. There is an ongoing PK study in CML patients with liver impairment.

4. Gender

Eighty-three males and sixty-four females were enrolled and randomized on the GIST trial. No obvious differences in the safety or efficacy profiles were noted between males and females. No obvious differences in the pharmacokinetic profile of the drug were noted between males and females.

5. Ethnicity

The majority of patients in the GIST trial were Caucasian (92.5%). No ethnic/racial specific analyses were conducted since the small numbers of patients who were not Caucasian would not permit a meaningful analysis.

6. Pregnancy

Imatinib should not be used in pregnant females. The drug is currently labeled as pregnancy class D, due to its teratogenic effects in rats and rat fetal loss after post-implantation exposure to doses of 60 mg/kg. No reports of exposure during pregnancy have been received in the postmarketing database.

APPEARS THIS WAY
ON ORIGINAL

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Clinical Development

Compound: Glivec® (Imatinib)/ Gleevec™ (Imatinib mesylate) [Formerly STI571].

Discussion of benefit and risk relationship and proposed post-marketing studies

Author:	Sandra L Silberman MD PhD
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1. Discussion of benefit/risk relationship

1.1. Benefit/risk relationship of current therapy

There is a clear medical need for an alternative effective therapy for patients with GIST for whom no effective standard therapy is available. Gleevec provides a new, effective and safe therapeutic option for these patients. Gleevec is a convenient oral medication, which is well tolerated. 40% of patients with malignant GIST treated with Glivec had a confirmed PR.

Gleevec is proposed for the treatment of inoperable and/or metastatic malignant GIST at a starting dose of 400 mg daily, a dose which is extremely well tolerated. It is recommended that a 600 mg dose be explored in those patients with an insufficient response to the starting dose.

The tolerability of Gleevec is especially profound when side effects are compared to conventional chemotherapy (which, as discussed below, is generally ineffective). Those AEs that may be related to the drug are generally limited to non-serious (CTC grade 1 or 2) cases of nausea, headache, diarrhea, fluid accumulation, rashes and fatigue. The finding that the rapid destruction of tumor tissue induced by Glivec could, in some patients, lead to serious intra-tumoral bleeding. Depending on the anatomical location of tumor lesions, this rapid destruction could result in GI, intra-abdominal or intra-hepatic hemorrhaging, however as shown in this patient cohort, no long term or irreversible effects of these complications ensued.

Both the long term safety and efficacy outcomes of chronic daily dosing with either 400 mg or 600 mg of Gleevec daily are unknown.

1.2. Benefit/risk relationship of alternative therapies

There is currently no effective therapy for inoperable and/or metastatic malignant GIST. Unfortunately, there has been no effective systemic therapy for unresectable or metastatic malignant GIST and attempted standard, soft tissue sarcoma therapies have proven futile. The response rates of GIST to any conventional chemotherapy ranges from 0-5% at best, a success rate much lower than that seen for other sarcomas of non-osseous tissue. GIST have proven to be relatively radioresistant as well. In a recently completed series on 143 patients whose GIST were defined by rigorous histopathologic, as well as immunohistochemical profiling, the overall objective response rate to conventional chemotherapy was 0%. In the same group of patients, the median time to progression following the first chemotherapy regimen was 1.5 months and the median time to treatment failure (TTF) was 1.2 months. Overall the median time to progression was less than two months for any regimen administered over the course of the disease. The median survival from the time of diagnosis was estimated to be 32.2 months and the median survival from the diagnosis of metastatic or recurrent disease was approximately 31 months. As a consequence of these poor responses to radiotherapy and/or chemotherapy, most GIST prove ultimately lethal.

1.3. Relative benefit/risk relationship

In terms of overall efficacy and relative safety, Gleevec has clearly demonstrable superiority over any conventional standard systemic therapy for this indication, which has been shown to have a response rate of 0%

Gleevec is the first small molecule protein tyrosine kinase inhibitor evaluated in a clinical setting shown effective as a rationally targeted therapeutic modality against GIST. For inoperable disease, no other therapeutic modality has demonstrated benefit, an indication that Gleevec is a breakthrough for these patients.

2. Proposed post-marketing studies

2.1. Post-marketing studies to collect safety data

Patients on study CSTI B2222 will be followed for a minimum of 24 months or until death, for further evaluation of safety as well as clinical outcomes. Two large phase 3 multinational clinical trials are being conducted independently for which additional information will be available to refine the current therapeutic recommendations; including the following safety information:

- relationship of dose to safety outcomes (short and long term dosing)
- relationship of demographics, including age, gender, disease parameters, prior therapy, ethnic background, to clinical outcomes and safety
- tolerance and/or resistance to therapy after long-term dosing

2.2. Post-marketing studies to extend the claim in the current indication

2.3. Post-marketing studies in other indications

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: imatinib mesylate
Proprietary Name: Gleevec™

Applicant: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936-1080

Drug Class: Antineoplastic

Indication:

Current: " Gleevec™ (imatinib mesylate) is indicated for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

The effectiveness of Gleevec™ is based on overall hematologic and cytogenetic response rates in CML (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival."

Proposed:

DRAFT

The effectiveness of Gleevec™ is based on overall hematologic and cytogenetic response rates in CML and objective response rates in GIST (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival."

Dosage and Administration

Current Label: "Therapy should be initiated by a physician experienced in the treatment of patients with chronic myeloid leukemia.

The recommended dosage of Gleevec™ (imatinib mesylate) is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis. The prescribed dose should be administered orally, once daily with a meal and a large glass of water.

Treatment should be continued as long as the patient continues to benefit.

Dose increase from 400 mg to 600 mg in patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematologic response after at least 3 months of treatment; loss of a previously achieved hematologic response."

Proposed Label: "Therapy should be initiated by a physician experienced in the treatment of patients with chronic myeloid leukemia or gastrointestinal stromal tumors. The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

DRAFT

The recommended dosage of Gleevec™ (imatinib mesylate) is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis. The recommended DRAFT mg/day for patients with unresectable and/or metastatic malignant GIST.

In CML, dose increase from 400 mg to 600 mg in patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematologic response after at least 3 months of treatment; loss of a previously achieved hematologic response.

DRAFT

B. State of Armamentarium for Indication(s)

Gastrointestinal stromal tumors (GIST's) are soft tissue sarcomas thought to arise from mesenchymal stem cells within the gastrointestinal (GI) tract. It is estimated that up to one third of all GISTs are malignant although their capacity for metastatic spread cannnot be clearly inferred from histopathologic features alone. Although GISTs may occur throughout the GI tract, they are usually located in the stomach and small intestine. (1)

The five-year survival for malignant GI mesenchymal tumors varies widely and has been reported anywhere from 30 to 80%. (2) Median survival of patients for whom complete surgical resection is not possible is in the range of 23 months. In a recent series of 143 patients with GIST defined by histopathologic as well as immunohistochemical profiling at the Dana Farber Cancer Institute, median survival from the time of diagnosis was estimated at 32.2 months. (3) In the literature, the median survival from the time of diagnosis of metastatic or recurrent disease has been reported between 19 and 31 months. (1, 2, 3)

No chemotherapy regimen has proven effective to date in the treatment of these tumors. Although the use of anthracycline-based regimens can result in response rates of 10-30% for a number of soft tissue sarcomas, the response rate of GISTs to such regimens has been reported to be 0-5% at best. (4, 5) In the series of 143 patients discussed, the overall objective response rate to chemotherapy was 0% and median time to progression following chemotherapy was 1.5 months. (3)

Radiation therapy has not been shown to be of any benefit in the treatment of GIST.

Advances in molecular biology and immunohistochemistry techniques now provide more specific criteria for the diagnosis of GIST based on the expression of the cell surface marker CD117 in addition to histologic considerations. (6) CD117 is an epitope on the extracellular domain of the transmembrane tyrosine kinase receptor Kit, the product of the proto-oncogene c-kit. (7) The expression of CD117 can be detected on the cell surface of malignant GIST tumor tissues in 95-100% of cases examined. It is hypothesized that virtually all of these tumors harbor mutations of the c-kit oncogene. Such mutations have been demonstrated in a number of CD117 positive GIST tumors. (8,9,10) The lack of demonstration of such a mutation in every malignant GIST tumor is possibly related to the limited number of mutations defined to date (new mutations are being characterized on an ongoing basis), as well as technical considerations such as the adequacy of samples used in the testing process.

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It also inhibits the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit.

The use of imatinib in a patient with a recurrent, metastatic GIST was first reported by Joensuu et al. in a 50 year old female. (11) Her tumor demonstrated staining for CD117 and she exhibited a response to imatinib 400 mg daily, which had been ongoing for 11 months at the time of publication of the case report.

Study B2222, the pivotal trial submitted in this sNDA, was initially designed as a pilot, proof-of-concept study for GIST patients in which two doses of imatinib were explored in an open label, randomized fashion (400 mg and 600 mg daily). The study was expanded to a total study population of 147 patients based on responses observed in the

initial conduct of the study and the lack of alternative treatment for patients with metastatic, recurrent disease. A preliminary report based on this study was presented at the American Society of Clinical Oncology (ASCO) meeting in April, 2001. (12)

Other clinical experience with the use of imatinib in patients with GIST includes a recently completed phase 1 dose escalation study conducted by the EORTC, also reported in preliminary fashion at ASCO and more completely in October, 2001. (13, 14) In this study, doses ranging from 300 mg daily up to 500 mg twice a day were studied in 36 patients with GIST and 4 patients with other soft tissue sarcomas. Dose limiting toxicity consisting of vomiting, nausea, edema, or dyspnea was encountered in 5 patients treated with 500 mg twice a day. It was concluded that 400 mg twice a day was well tolerated in this population. In addition, both the NCI and the EORTC are independently conducting multicenter trials of STI571 400 mg/day or 800 mg/day in patients with GIST. The intergroup study sponsored by the NCI was closed to enrollment in September, 2001 after accrual of more than 700 patients.

References are listed in the literature review section (IV. D.)

C. Important Milestones in Product Development

5/10/01 Gleevec™ (imatinib mesylate)was approved in the United States (NDA 21-335) for treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

3/07/01 The sponsor submitted a briefing book for an End-of Phase ½ (EOP2) meeting. This submission outlined a supplemental registration proposal for imatinib in the treatment of patients with unresectable or metastatic malignant gastrointestinal stromal tumors (GIST). It proposed the submission of data from protocol B2222, a multicenter, open-label randomized phase 2 study of two different doses of imatinib in this population with endpoint data for time to treatment failure, rate of confirmed responses, and survival. Full PK profiles on 10 patients at each dose level, and full safety information from the study would be submitted, in addition to summary data from a corresponding control group of GIST patients compiled from a single center database.

3/21/01 FDA responses to the sponsor's EOP2 questions submitted in the briefing package were sent. FDA stated that response rate and response duration were preferred endpoints over time to treatment failure or time to progression. The sponsor was reminded that the historical database population should have a light microscopic appearance compatible with GIST in addition to CD117 (c-kit) positivity. The Agency commented that

FDG-PET tumor assessments would be interesting but could not replace traditional radiologic tumor evaluation methods at this time.

3/27/01 The EOP2 meeting originally scheduled for 3/27/01 was cancelled since the sponsor felt there was no need for further discussion.

4/4/01 Additional statistical comments were sent to the sponsor. These emphasized the need to set up an efficacy criterion for the lower limit of an exact two-sided 95% confidence interval for the response rate. The intent-to-treat (ITT) analysis would be considered the primary analysis of interest.

7/12/01 The preNDA responses from FDA were forwarded to the sponsor. These included a request for submission of baseline and best response x-rays 'for all responders.' The FDA asked the sponsor to clarify the status of the c-kit assay with respect to commercial availability and ability to quantitate c-kit expression. The preNDA meeting originally scheduled for 7/17/01 was cancelled since the responses required no further clarification per the sponsor.

9/19/01 In a teleconference with the sponsor, the FDA conveyed the importance of designation of a reference laboratory and subsequent development of a commercial assay for c-kit expression testing in the case of FDA approval of imatinib for patients with GIST.

Protocol B2222 Amendments

Amendment #1 was released on 9/05/00 and included the following changes:
Update of the introduction section to include further clinical data from patients with CML and PK data from 2 patients with GIST receiving imatinib.
Expansion of the number of patients to be enrolled to 33 patients per treatment arm (66 total) based on preliminary response data.
A recommendation of prophylactic loperamide use for grade ½ diarrhea prior to dose reduction/interruption.

Amendment #2 was released on 10/27/00 and included further expansion of the number of patients to be enrolled to 60 per treatment arm (120 total). Details on tumor assessment were modified to call for sponsor recalculation of investigator assessments and for use of the sponsor's assessment for the primary analysis.

Amendment #3 was released on 11/27/00 and further expanded patient enrollment to 100 per treatment arm (200 total).

Amendment #4 was released on 12/22/00 and modified eligibility to permit patients with ECOG performance status 3 to be enrolled in the study.

D. Other Relevant Information

As of October 3, 2001, imatinib mesylate is approved in 32 countries including the United States for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. The current new indication being sought in this supplemental NDA is the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

E. Important Issues with Pharmacologically Related Agents

No issues exist.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology and biopharmaceutics review indicates that the submitted final study report of the simvastatin drug interaction study in patients with CML receiving Gleevec™ affirms the prior conclusion from an interim analysis that imatinib increases simvastatin exposure (approximately a 2-fold increase in Cmax and a 3.5-fold increase in AUC). This information is already included in the package insert and no change is recommended.

The review also recommends the addition of the following statement to the clinical pharmacology section of the label : " The pharmacokinetics of imatinib in CML and GIST patients are similar ."

B. Statistics

This is a combined medical/statistical review. The statistical reviewer's analyses and comments are incorporated into this document. (see Integrated Review of Efficacy)

C. Chemistry

The chemistry review notes no change in the imatinib mesylate formulation, strength, or packaging size. The sponsor's request for a categorical exclusion from the preparation of an environmental assessment is granted

D. Animal Pharmacology and Toxicology

No animal pharmacology and toxicology review was conducted for this supplemental NDA as there was no new data submitted.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML), and the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit.

The pharmacokinetic characteristics of the drug have been described in the NDA approved on 5/10/01 for the CML indication. The approved dosage form for CML was used in the GIST program (100 mg capsules) and is proposed for marketing in GIST using 400 mg or 600 mg orally, daily. The human PK and bioavailability program for GIST consists of one clinical study with PK assessment in patients with GIST and one drug-drug interaction study with simvastatin in patients with CML that was completed in the interim since the original NDA.

Basic PK Properties:

In healthy subjects and population pharmacokinetic studies in over 500 patients with CML, imatinib was well absorbed after oral administration. Cmax was achieved within 2-4 hours post dose. Following oral administration in healthy volunteers, the elimination half-life of imatinib was approximately 18 hours. Mean AUC increased proportionally with increasing dose over the range 25-1000 mg. There was no significant change in the pharmacokinetics on repeat dosing.

In GIST patients receiving once daily dosing (n=10 at 400 mg and n=9 at 600 mg), imatinib was rapidly absorbed. Mean terminal half-life after the first dose was 15.8 hours at 400 mg and 14.5 hours at 600 mg. The pharmacokinetics of imatinib in CML and GIST patients are similar. Elimination of imatinib is predominantly in the feces, mostly as metabolites.

Drug-Drug Interactions:

In the drug interaction study with simvastatin in CML patients, imatinib increased the mean Cmax and AUC of simvastatin by 2-3 fold indicating an inhibition of CYP3A4 by imatinib. Therefore imatinib can increase the exposure to co-medications that are substrates of CYP3A4.

There was a significant increase in exposure to imatinib in healthy subjects when the drug was co-admininistered with a single dose of ketoconazole (mean Cmax increased by 26% and AUC increased by 40%).

Hepatic and Renal Impairment:

Imatinib and its metabolites are not excreted via the kidney to any significant extent. No specific studies have been performed in patients with impaired renal function.

Exposure to imatinib may be expected to be increased if liver function is impaired. No specific studies have been completed in patients with impaired liver function, however, a PK study in CML patients with liver impairment is currently underway.

Special Populations:

There is no effect of gender on the kinetics of imatinib in patients with CML or GIST.

In patients with CML, imatinib clearance appears to increase with increasing body weight such that for a patient weighing 50 kg, the mean clearance is expected to be 8.5 L/h, whereas for a patient weighing 100 kg the clearance will rise to 11.8 L/h. These changes are not considered sufficient to warrant dose adjustment based on body weight. In patients with GIST, no significant effect of body weight on clearance is evident.

Population Pharmacokinetics

Population PK modeling attempted to attribute interpatient PK variability to patient characteristics. Sponsor and FDA modeling indicated that no patient attributes could reasonably explain interpatient variability in PK parameters. (see biopharmaceutics review for further information)

B. Pharmacodynamics

In the phase 1 study of patients with CML (previously reviewed in the NDA for imatinib mesylate in the treatment of CML), a complete hematologic response (WBC $< 10 \times 10^9$/L by day 28) was observed in all patients studied with PK and PD samples at daily doses $\geq$ 400 mg. Simulations from the Emax model of these parameters predicted that a daily dose of 400 mg would lead to full normalization of WBC in 76% of patients.

IV. Description of Clinical Data and Sources

A. Overall Data

NDA 21-335/S01 contains the primary data from Study B2222, which was conducted in 3 centers in the United States and 1 center in Finland. Summary information from a retrospective analysis of a database describing 143 patients with mesenchymal tumors arising from the GI tract that fulfilled the criteria for the diagnosis of GIST and who were followed at a multidisciplinary cancer center (the Dana Farber Cancer Institute) from January 1996 to March 2001 was also included in the submission to give a historical context.

B. Table Listing the Clinical Trials

Table 1 lists the clinical trials of imatinib submitted to this supplemental NDA. The development program in the GIST indication was limited to a single randomized phase 2 trial in patients with inoperable or metastatic GIST expressing c-kit (protocol B2222). A clinical trial of imatinib in patients with CML to examine interactions with simvastatin has been completed since the original NDA and the study report was submitted to this supplemental application (protocol 0118).

Table 1 : Clinical Trials Submitted to sNDA

Protocol	Country	Enrollment Dates	Population, N	Primary Endpoint
B2222	U.S./Finland	7/00 ongoing	GIST, 147	Response Rate
0118	U.K.	10/30/00 to 1/17/01	CML, 20	Safety, PK

C. Postmarketing Experience

The Office of Drug Safety (ODS) was consulted to conduct a post marketing safety review. Specifically, ODS was asked to review the AERS database for cases of hemorrhage in non-leukemia patients being treated with imatinib and for cases of sudden death in patients who were also receiving cardiovascular drugs. All three cardiac arrhythmia cases included concomitant or possibly precipitating noncardiac adverse events. Among the 12 cases of hemorrhage in patients being treated for non-leukemia cancers, only one had bleeding from a site other than the tumor or gastrointestinal tract. This patient was also taking warfarin, which is known to interact with imatinib. The conclusion of the ODS safety officer, Kate Phelan, R.Ph., is that 'the AERS cases of cardiac arrhythmia and hemorrhage in patients receiving imatinib neither strongly support nor refute an association between these events and the drug.'

D. Literature Review

The sponsor submitted an extensive literature reference list which includes most of the references listed below as well as others. References 7 and 14 were reviewed by the medical officers but were not included in the sponsor's literature review. Reference 14 was published subsequent to the submission of this sNDA.

1. Pidhorecky I, Cheney RT, Kraybill WG et al. Gastrointestinal stromal tumors: current diagnosis, biologic behaviour, and management. *Ann Surg Oncol* 7:705-712, 2000.
2. Casper ES. Gastrointestinal Stromal Tumors. Curr Treat Options Onc 1:267-273, 2000.
3. Goss GA et al. Clinical features and lack of response to conventional therapies of metastatic and advanced gastrointestinal stromal tumors (GIST) defined by the KIT receptor tyrosine kinase (CD117). In preparation
4. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: Recent advances in understanding of their biology. Human Pathology 30:1213-1220, 1999.
5. DeMatteo RP, Lewis JJ, Leung D et al. Two hundred gastrointestinal stromal tumors: Recurrence patterns and prognostic factors for survival. Annals of Surgery 231:51-58, 2000.
6. Hirota S, Osozaki K, Moriyama Y et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 279:577-580, 1998.
7. Ashman LK. The biology of stem cell factor and its receptor c-kit. Int Journal of Biochem Cell Biology 31:1037-1051, 1999.
8. Lasota J, Jasinski M, Sarlomo-Rikala M et al. Mutations in exon 11 of c-kit occur preferentially in malignant versus benign gastrointestinal stromal tumors and do not occur in leiomyomas or leiomyosarcomas. Amer Jour Pathol 154:53-60, 1999.
9. Taniguchi M, Nishida T, Hirota S et al. Effect of c-kit mutation on prognosis of gastrointestinal stromal tumors. Cancer Res 59:4297-4300, 1999.
10. Lux ML, Rubin BP, Biases TL et al. Kit extracellular and kinase domain mutations in gastrointestinal stromal tumors.Am J Pathol 156:791-795, 2000.
11. Joensuu H, Roberts PJ, Sarlomo-Rikala M et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. NEJM 344 (14):1052-1056, 2001.
12. Blanke CD, von Mehren M, Joensuuu H et al. Evaluation of the safety and efficacy of an oral molecularly-targeted therapy, STI571, in patients (Pts) with unresectable or metastatic gastrointestinal stromal tumors (GISTS) expressing c-kit (CD117) Proc ASCO 2001, page 1a (abstract #1).
13. Van Oosterom AT, Judson I, Verweij J et al. STI571, an active drug in metastatic gastrointestinal stromal tumors (GIST), an EORTC phase 1 study. Proc ASCO 2001, page 1a (abstract #2).
14. Van Oosterom AT, Judson I, Verweij J et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. Lancet 358:1421-1423, 2001.

15. Green S, Weiss GR. Southwest Oncology Group standard response criteria: endpoint definitions and toxicity criteria. Investigational New Drugs 10:239-253, 1992.

V. Clinical Review Methods

A. How the Review was Conducted

The efficacy review is based primarily on data from the randomized trial B2222 in patients with metastatic or unresectable GIST.

B. Overview of Materials Consulted in Review

The following materials were reviewed by the medical and statistical officers:

- The regulatory history of the application
- The 2001 review of Gleevec™ in patients with CML
- IND #[redacted]
- Electronic submission of the sNDA
- Relevant published literature
- Copies of radiology studies for responders on study B2222

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Baseline and best response radiology studies for responders were requested by the FDA in a communication to the sponsor forwarded 7/12/01. Copies of radiology studies obtained at baseline and at best response for 90 patients were submitted by the sponsor and reviewed by the medical officers Ramzi Dagher and Martin Cohen. At the time of sNDA submission, it was apparent that the sponsor was claiming a confirmed partial response in fewer patients (N=59) than the 90 patients whose radiology studies were submitted. The FDA requested a clarification of the difference between the numbers submitted and responses claimed and the sponsor explained that radiology studies had been submitted for 31 patients with an unconfirmed response and 59 patients with a confirmed partial response. The medical reviewers used the same criteria for assessment of response as outlined in the protocol (See appendix describing SWOG criteria) and agreed with the sponsor's assessment of a confirmed partial response in 40 patients. Radiology studies of the remaining 19 of 59 sponsor claimed responses were reviewed by Dr. Ronnelle Dubrow, MDACC due to the discrepancy between the sponsor's assessment and that of the medical reviewers.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Study B2222 was conducted in accordance with the Declaration of Helsinki, US21 Code of Regulations dealing with clinical studies, Directive 91/507/EEC of

the European Community, and ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. The protocol and its amendments were reviewed and approved by Institutional Review Boards. Written informed consent was required prior to patient enrollment on the trial.

E. Evaluation of Financial Disclosure

Sasa Dimitrijevic, Ph.D., Novartis Pharmaceuticals states in item 19 section 4 of volume 1 that " No principal investigators are full or part-time employees of Novartis Pharmaceuticals Corporation. No disclosable financial information was reported by any of the investigators participating in the trials listed on the spread sheet(s)." A form OMB No. 0910-0396 certified by David Parkinson, M.D., V.P. for Clinical Research and Development, Novartis Pharmaceuticals is included in the submission. All principal investigators responded to the sponsor's inquiry in this regard.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The results of a single, phase 2 , open label randomized multicenter study of imatinib mesylate in patients with unresectable and/or metastatic GIST were submitted. Efficacy results according to the sponsor's analysis indicate an objective response rate of 40% (59/147) at the time of data cut-off for the study report. According to the sponsor, the response rate for the 400 mg dose group is 37% (27/73) and for the 600 mg dose group it is 43% (32/74). The medical reviewers' assessment of response rates differs slightly from the sponsor, with a confirmed overall partial response in 38% (56/147) of patients at the cut-off date. Response rates were 33% (24/73) and 43% (32/74) for the 400 mg and 600 mg dose groups respectively. The sponsor and the reviewers agree that no confirmed complete responses were observed.

No correlation between dose and response was observed, although the study was not powered to detect a difference in response rates between the two dose levels examined.

Duration of response ranged from seven to 38 weeks, according to the sponsor, with only one out of 59 patients who achieved a confirmed PR having progressed by the cut-off date. The reviewers' analysis also indicates a duration of response range of 7 to 38 weeks with only one of 56 patients with a confirmed PR having progressed by the cut-off date. However, the relatively short duration of followup limits the ability to draw definitive conclusions regarding the durability of responses to imatinib in GIST patients.

Overall survival was not analyzed. There was only a small number of deaths observed on study and a relatively short period had elapsed from recruitment to the cutoff date for data submission.

B. General Approach to Review of the Efficacy of the Drug

The efficacy database consists of a single, open label phase 2 study of imatinib in patients with metastatic or unresectable gastrointestinal stromal tumors (GIST) who were randomized between two dose levels.

C. Detailed Review of Trials by Indication

The efficacy review is based primarily on one multicenter trial of imatinib titled:

Open, Randomized, Phase 2 Study of STI571 in Patients with Unresectable or Metastatic Malignant Gastrointestinal Stromal Tumors Expressing c-kit.

1. Protocol Review

Table 2 lists the principal investigators and the corresponding participating institutions.

Table 2 : Principal Investigators and Address

Investigator Name	Address
Dr. Charles Blanke	Oregon Health Sciences University Oncology MC OP28 3180 SW Sam Jackson Park Road Portland OR 97201, USA
Dr. George Demetri	Dana Farber Cancer Institute 44 Binney Street (G-530) Boston MA 02115, USA
Dr. Joensuu Heikki	Department of Oncology Helsinki University Central Hospital Haartmaninkatu 4, POB 180 FIN-00240 Helsinki, Finland
Dr. Roger McLennan	Geelong Hospital Ryrie Street Geelong 3220, Australia
Dr. Margaret von Mehren	Fox Chase Cancer Center 7701 Burlhome Avenue Philadelphia PA 19111, USA

Reviewer Comment : One patient initially enrolled at the Dana Farber Cancer Institute transferred his care to Dr. McLennan in Australia. All other patients were enrolled and followed in the 3 U.S. centers and the center in Finland.

Table 3 : Protocol Milestones

Milestone	Date	Comments
Protocol open	7/2000	Originally a pilot proof of concept study with randomization to 400 or 600 mg imatinib daily.
First patient enrolled	7/6/00	N/A
Amendment #1	9/05/00	Expanded enrollment from 18/arm to 33 /arm based on preliminary response data. Prophylactic use of loperamide was recommended for grade ½ diarrhea prior to dose reduction/interruption.
Amendment #2	10/27/00	Expanded enrollment to 60 /arm. No-go criterion for dose level rejection if <5 responses/arm was replaced by use of confidence intervals. Details on tumor assessment modified to call for sponsor recalculation of investigator assessments.
Amendment #3	11/27/00	Expanded enrollment to 100 /arm
Amendment #4	12/22/00	Allow enrollment of ECOG PS3
For this report	N/A	Analysis of response duration replaced TTP. Minimum treatment duration of 3 weeks was dropped from the definition of the efficacy analyzable population.
Data Cutoff Date	7/10/01	N/A
sNDA submitted	10/15/01	N/A

Objectives:

* To assess the clinical and biological activity of Gleevec™ (imatinib mesylate) in patients with unresectable or metastatic malignant GIST, as judged by objective response rates.
* To assess the safety and tolerability of imatinib in this population.
* To evaluate the pharmacokinetic profile of imatinib in this population.
* To assess the impact of imatinib in this population by evaluation of time to progression and overall survival.
* To evaluate in selected patients the histopathologic effects of imatinib treatment on GIST, including 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.
* To evaluate in selected patients the correlation between c-kit mutations and clinical outcome.

Selection Criteria

Inclusion Criteria

- Age $\geq$ 18 years
- Histologically documented diagnosis of GIST that is malignant as well as unresectable and/or metastatic and therefore incurable with any conventional multimodality approach.
- Immunohistochemical documentation of c-kit (CD117) expression by tumor.
- At least one site of measurable disease (as defined by Southwest Oncology Group Solid Tumor Response Criteria) that has not been previously embolised or irradiated.
- ECOG performance status 0-3.
- Adequate end organ function defined as follows:

  Total bilirubin < 1.5 x ULN, SGOT and SGPT < 2.5 x ULN (or <5 x ULN if hepatic metastases are present), creatinine < 1.5 x ULN, ANC > 1.5 x 10^9/L, platelets > 100 x 10^9/L.

- Female patients of childbearing potential must have a negative pregnancy test within 7 days before initiation of study drug dosing. Post menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Male and female patients of reproductive potential must agree to employ an effective barrier method of birth control throughout the study and for up to 3 months following discontinuation of study drug.
- Life expectancy of at least 6 months.
- Written, voluntary, informed consent.

Reviewer Comment : The inclusion criteria originally allowed for performance status (PS) 0-2 only. Amendment # 4 changed the criteria to allow for PS 0-3.Only one patient with PS 3 was enrolled in the study.

Exclusion Criteria

- Patient has received any other investigational agent within 28 days of first day of study drug dosing.

- Patient is < 5 years free of another primary malignancy except : if the other primary malignancy is not currently clinically significant nor requiring active intervention and Novartis' approval is obtained, or if other primary malignancy is a basal cell skin cancer or a cervical carcinoma in situ. Existence of any other malignant disease is not allowed.

Reviewer Comment : This modification was made as a component of amendment #3

- Patient with grade III/IV cardiac problems as defined by the New York Heart Association Criteria (i.e. congestive heart failure, myocardial infarction within 6 months of study).
- Female patients who are pregnant or breast-feeding.
- Patient has a severe and/or uncontrolled medical disease (i.e. uncontrolled diabetes, chronic renal disease, or active uncontrolled infection). Patient has a known brain metastasis.
- Patient has an acute or known chronic liver disease (i.e. chronic active hepatitis, cirrhosis).
- Patient has a known diagnosis of human immunodeficiency virus (HIV) infection.
- Patient received chemotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin-C) prior to study entry.
- Patient previously received radiotherapy to $\geq$ 25% of the bone marrow.
- Patient had a major surgery within 2 weeks prior to study entry.
- Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.

Treatment Plan

Patients were randomized to receive imatinib either 400 mg orally once a day or 600 mg orally once a day for an exposure period of no more than 24 months provided that, in the opinion of the investigator, the patient is benefiting from treatment with imatinib and in the absence of any safety concerns.

Patients were instructed to keep normal eating habits. However, low-fat breakfast was recommended, avoiding xanthine (e.g. caffeine) or grapefruit containing food or beverages. STI571 is a local irritant and the following instructions were provided : Drug must be taken in a sitting position with a large glass of water (250 ml). A minimum of 1 hour should be allowed between last drug intake and going to bed.

Reviewer comment : The recommendation to take the drug in a sitting position with a large glass of water was based on the drug's known irritant effect on the GI tract. Since no information concerning food interaction was available at the time when the protocol was written, the original protocol required that the drug should be taken 2-3 hours after breakfast. According to the sponsor, "when it was demonstrated that food had no relevant effect on the PK behaviour of Gleevec™ (studies 0109 and 0110), the protocol was amended to advise patients to take Gleevec™ in the morning with a low-fat breakfast devoid of xanthine or grapefruit containing foods and beverages." (see volume 7, Background and overview of clinical investigations, section 2 clinical pharmacology considerations on page 5).

Prophylactic use of loperamide was recommended for patients who experienced grade 1 or 2 diarrhea before resorting to dose interruption for diarrhea.

Reviewer Comment : Prophylactic use of loperamide in patients who developed grade ½ diarrhea was added as a component of amendment #1.

Dose modifications for non-hematologic toxicity provided in the protocol

If the patient experiences a Grade 2 non-hematologic toxicity, study drug must be withheld until the toxicity has resolved to ≤ Grade 1. Imatinib may then be resumed at the same daily dose. If the Grade 2 toxicity recurs, imatinib must be withheld until the toxicity has resolved to ≤ Grade 1, and the daily dose must be reduced to 300 mg once daily for patients initially treated with 400 mg of imatinib or to 400 mg for patients initially treated with 600 mg of imatinib.

If the patient experiences grade ¾ toxicity, study drug must be withhheld until the toxicity has resolved to ≤ Grade 1 and the daily dose must be reduced to 300 mg once daily for patients initially treated with 400 mg of imatinib or to 400 mg for patients initially treated with 600 mg of imatinib. If the Grade ¾ toxicity recurs, imatinib must be withheld until the toxicity has resolved to ≤ Grade 1, and the daily dose must be reduced, to 200 mg once daily for patients initially treated with 400 mg of imatinib or to 300 mg once daily for patients initially treated with 600 mg.

Dose modifications for hematologic toxicity provided in the protocol

If a patient experiences a Grade ¾ hematologic toxicity, imatinib must be withheld until the toxicity has resolved to ≤ Grade 2. If the toxicity resolves within two weeks, imatinib treatment may be resumed at the same dose. If the Grade ¾ toxicity recurs or persists for longer than two weeks, imatinib must be withheld and then recommenced at the daily dose of 300 mg once daily for patients treated with 400 mg of STI571 or at 400 mg for patients treated with 600 mg of imatinib, once toxicity has resolved to ≤ Grade 2.

No dose reductions will be performed for grade ¾ anemia. If the patient develops anemia, he/she may be transfused at the discretion of the investigator.

Other dose modifications outlined in the protocol

The optimal dose of imatinib in GIST is unknown, and the presence of a clinically relevant dose-response was suspected at study initiation. It was believed that a higher dose might induce a response even if a lower dose failed. This study made it possible for patients on the lower dose to (400 mg daily) to increase to the higher dose level (600 mg daily) if there was evidence of disease progression and the patient remained in otherwise good clinical condition. Novartis and all study investigators had to agree to the dose increase in each patient. Patients who progressed on 600 mg daily would be discontinued from the study.

If vomiting occurs, no additional trial medication should be taken that day.

If for any reason, treatment with imatinib was interrupted for 14 days or more, approval from Novartis was required before continuing treatment.

Safety Considerations

Clinical Studies

A complete medical history (relevant medical history, prior antineoplastic treatment, disease history, cancer related symptoms, prior concomitant medications) and physical examination was planned at the first visit (within the week preceding initiation of study drug). Body weight was to be measured weekly during the first month of treatment, every other week during the second month, and monthly thereafter while on study. A physical examination and vital signs were to be repeated at the beginning of months 2, 4, 7, 14, 19 and 25.

Reviewer comment : In CML patients treated with imatinib, onset of fluid retention was observed early on in the course of therapy, i.e. within the first 2 months of drug initiation in most patients. This explains the relatively frequent body weight measurements outlined in this protocol for the first two months of treatment.

Laboratory Studies

Hematology assessment including CBC with differential and platelet count were planned at screening, weekly during the first month, every other week during the second month, and monthly thereafter. Blood chemistry assessment that included creatinine, BUN or urea, uric acid, albumin, total protein, total bilirubin, alkaline phosphatase, AST, ALT, and LDH.
was planned using the same schedule.

Pharmacodynamic Assessments

All pharmacodynamic assessments listed below (FDG-PET, Dynamic MRI, Research blood/serum samples, and serial tumor biopsies) were considered optional, to be conducted at each investigator's discretion.

FDG-PET

Based on the putative mechanism of action of the drug, it is possible that a change in the metabolic profile of the tumor will be detectable before any tumor response will occur. In order to investigate this possibility, a fluorodeoxyglucose PET scan was an optional measure to be performed at baseline and after one month of treatment.

Dynamic MRI

Tumor vascular permeability and blood flow were to be assessed at the investigator's discretion and whenever possible using a dynamic MRI procedure with contrast agent injection.

Research blood/serum samples

Imatinib inhibits VEGF induced angiogenesis. It is currently not known whether imatinib therapy will reduce circulating VEGF levels and whether serum or whole blood VEGF levels can be used to monitor treatment efficacy in GIST. Whole blood and serum collections were planned at baseline, at times of response evaluation, and when progressive disease was detected. At each time point, 2 ml of whole peripheral venous blood and 1 ml of serum was required for these analyses.

Tumor biopsies (fresh and fixed)

Imatinib is expected to affect the phosphorylation status of KIT and other receptor tyrosine kinase targets and downstream cell signaling effectors in malignant GIST cells in vivo. To explore this change and other histopathologic changes in tumor tissue, a tumor biopsy sample was to be obtained at baseline (within 2-4 weeks before starting study drug) and again after 2-4 weeks of study drug dosing. Subsequent samples were to be obtained as feasible. Samples were to be obtained using core needle biopsy and studied as follows:

1. routine histopathology
2. immunohistochemical analysis (including CD117 [KIT])
3. phosphorylation status of c-kit and other tyrosine kinases
4. c-kit mutation analysis and assays of cell proliferation/apoptosis

Response Evaluation

Tumor evaluation was performed at baseline and at the beginning of months 2, 4, 7, 14, 19, and 25 (end of study). Assessments were performed by MRI or CT scan throughout the study. If possible, a single radiologist was to perform all evaluations for an individual patient. Radiological studies were to account for all lesions that were present at baseline and must have used the same techniques as used at baseline. All tumor assessments were to be performed within 14 days of the scheduled day of assessment.

Tumor response was defined by the Southwestern Oncology Group (SWOG) solid tumor response criteria (See Appendix section XI.A). (14) All known disease (measurable, evaluable, and nonevaluable) was to be accounted for when assessing objective tumor status. All complete and partial responses must have been confirmed by a second assessment at least 4 weeks later.

Statistical Methods

After expansion of planned enrollment by amendments 1-3, approximately 200 patients were to be randomized to one of two treatment arms (imatinib 400 mg or 600 mg daily dose) upon entry into this phase 2, open label trial.

Reviewer comment : Enrollment was stopped after 147 patients were enrolled as it was apparent that a threshold of response > 10% (lower bound) had been reached.

The safety analyzable population included all patients who received at least one dose of trial medication. The intent to treat (ITT) population included all enrolled patients who received at