

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: NDA 21-335

MEDICAL REVIEW

Executive Summary

Clinical Review of a New Drug Application

From: Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

Drug: GleevecTM (imatinib mesylate capsules)
Applicant: Novartis Pharmaceuticals
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This document summarizes the DODP clinical review findings and recommendations to the Office of Drug Evaluation I in FDA's Center for Drug Evaluation and Research.

I. Recommendations

A. Recommendation on Approvability

FDA's Division of Oncology Drug Product (DODP) recommends approval of Gleevec™ (imatinib mesylate capsules) for treating chronic myelogenous leukemia (CML) in three clinical settings (listed below). We recommend approval 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 recommended indications are treatment of the following phases of CML:

- 1) blast crisis (CML BC)
- 2) accelerated phase (CML AP)
- 3) chronic phase after failure of interferon-alpha therapy (CML CP)

The following paragraphs summarize DODP's view on the benefits and risks of imatinib for the recommended indications.

The finding of benefit is based on the surrogate endpoints hematologic response (HR), complete hematologic response (CHR), major cytogenetic response (MCyR), and complete cytogenetic response (CCyR). These are defined in section II of this document. Surrogates supporting accelerated approval for each indication are:

<u>Indication</u>	<u>Surrogate endpoint(s)</u>
CML CP	MCyR and CCyR
CML AP	HR, MCyR, and CCyR
CML BC	HR

The efficacy results in each indication are summarized in section II. For each indication, DODP determines that the effect of imatinib treatment measured by these surrogates is either better than available therapy or is similar to available therapy, and that toxicity is less.

It is important that physicians and patients understand that the known risks of treatment with imatinib and understand that additional toxicities from chronic treatment may yet be discovered.

FDA review determined the following areas of concern:

- **Edema and fluid retention.** Most patients have superficial edema and some patients have more serious and rarely life-threatening fluid retention.
- **Cytopenias.** Imatinib decreases the number of white blood cells and platelets, increasing the risk of infection and bleeding. Oncologists are familiar with this problem from experience using cytotoxic chemotherapy but must be aware that this also occurs with imatinib.
- **Liver toxicity.** Animal studies and clinical data demonstrate hepatic toxicity. Although only one death was definitely attributed to imatinib therapy (in a patient taking acetaminophen), serious toxicity may result if liver tests are not closely monitored.
- **Drug-drug interactions.** Significant drug-drug interactions have been observed with imatinib. Imatinib is metabolized by, and also inhibits, hepatic P450 isoenzyme CYP3A4. Significant clinical problems attributed to interactions with imatinib were reported in patients receiving warfarin and dilantin.
- **Potential immunosuppression.** Imatinib causes lymphopenia in animals and humans. In addition, chronic studies in monkeys showed recrudescence of endemic dormant malaria. We do not yet have chronic data in humans to know whether these findings will translate into an increase risk of infections (e.g., opportunistic infections) in humans.

As outlined above, there are expected benefits and there are known and potential risks from treatment with imatinib for the recommended indications. For each indication, it is the clinical judgement of the Division of Oncology Drug Products (DODP) that the potential benefits outweigh the risks.

However, we also realize that imatinib may be prescribed for indications not recommended in the approved label (e.g., for initial treatment of CML, in patients who will live, on average, five to seven years). FDA and Novartis must communicate to physicians the known and potential risks of treatment with imatinib and the limits of current clinical data on chronic use of imatinib. Patients and physicians should also be informed about the limited follow-up on patients treated chronically with imatinib. Novartis should promptly and carefully evaluate and report new safety data from ongoing trials and spontaneous reports, and in conjunction with FDA, the information should be efficiently communicated to physicians and patients.

B. Recommendations on Phase 4 Studies.

1. Binding phase 4 commitments under accelerated approval

Under the accelerated approval regulations, the sponsor must conduct trials to demonstrate that imatinib provides clinical benefit in the treatment of CML. The sponsor will be required to:

- Complete follow-up on the NDA trials 102 (BC), 109 (AP), and 110 (BC).
- Conduct and submit the final study report for Protocol 106 (a trial comparing imatinib versus interferon-alpha in patients with newly diagnosed previously untreated CML).

Collectively, these trials have the potential to demonstrate clinical benefit in populations representing (or closely related to) the three indications we recommend for accelerated approval.

2. Other phase 4 commitments

Novartis agreed to these additional phase 4 commitments:

a. Commitment to do pediatric studies

Because imatinib is an Orphan Drug, pediatric studies are not mandated under the Pediatric Rule. However, Novartis agreed to perform a phase I study in children with refractory/relapsed Ph+ leukemias and a phase 2 efficacy study in an appropriate pediatric population.

b. Commitments to evaluate imatinib pharmacokinetics and drug interactions

Novartis made several commitments to evaluate imatinib pharmacokinetics and drug interactions:

- i. Conduct and submit final study reports for hepatotoxic drug interactions (e.g. with acetaminophen).
- ii. Conduct and submit an in vivo study of drug interactions involving CYP2D6 .
- iii. Implement a physician and patient education program regarding use of concomitant medications with STI571 (CYP3A4 and 2D6 interactions).
- iv. Assess potential drug interaction between imatinib and a substrate of CYP2D6. The protocol should be submitted to the FDA for review.
- v. Conduct a pharmacokinetics study with imatinib in subjects or patients with liver impairment. The study protocol should be submitted for FDA review.
- vi. Assess the plasma protein binding of the major metabolite of N-demethylated piperazine derivative of STI571. (This is an active metabolite with AUC = 16%X AUC of parent drug. If plasma protein binding of this metabolite is low, it may be a clinically significant variable to consider in future studies.)

vii. Meet with FDA's Division of Oncology Drug Products within 2 months of approval to discuss plans and commitments to evaluate the etiology and treatment of the imatinib fluid retention syndrome.

II. Summary of clinical findings

A. Overview of Clinical Program

Imatinib (Gleevec®, STI571) represents a new class of drugs designed to inhibit enzymes involved in cancer growth. Imatinib was designed to inhibit the Bcr-Abl kinase, an aberrant enzyme produced by malignant white blood cells in patients with chronic myelogenous leukemia (CML). This targeted kinase is the protein produced by a DNA translocation (the "Philadelphia chromosome") that appears central to the CML disease process. Although the intended target is unique to CML cells, treatment effects are not entirely selective. Laboratory evidence suggests imatinib inhibits other tyrosine kinases, and clinical data from this NDA show that imatinib does have important side effects in humans.

CML progresses through several clinical phases over an average of five to seven years:

- chronic phase (about 4-5 years)
- accelerated phase (about 1 year)
- and blast crisis (about 3-6 months)

During the chronic phase of CML, disease can usually be managed with hydroxyurea and alpha interferon with or without cytosine arabinoside. No studies were submitted for treatment of early chronic phase CML. Novartis submitted studies supporting imatinib for treatment of three CML indications:

- Study 110 is a single arm study in 532 patients *in chronic phase CML failing treatment with alpha interferon.*
- Study 109 is a single arm study in 235 patients with *accelerated phase CML.*
- Study 102 is a single arm study in 260 patients with *CML in blast crisis.*

B. Efficacy

Efficacy is discussed in 2 sections. In the first section, we discuss the regulatory meaning of efficacy in CML. In the second section, efficacy results are summarized and interpreted from a regulatory perspective.

1. The regulatory meaning of efficacy in CML

For each CML treatment indication proposed by Novartis, DODP considered approval of imatinib by two regulatory routes, *traditional approval* and *accelerated approval*. As

outlined below, the evidence needed to demonstrate efficacy differs for these two mechanisms of approval.

a. Efficacy under traditional approval

Traditional NDA approval requires the demonstration of clinical benefit. FDA is responsible for determining which clinical endpoints measure clinical benefit. In oncology, survival and tumor-related symptoms are accepted as clinical benefit. Other endpoints are evaluated in the context of the clinical setting. Whether FDA judges endpoints such as objective tumor response to be clinical benefit depends on the toxicity of treatment, the tumor type, the efficacy of available therapy, the response rate, the response type (CR versus PR), the response duration, and supportive data on symptom improvement. In the past decade DODP has approved five drugs for treating hematologic diseases based on non-randomized trials. The endpoints supporting approval were complete response (pentostatin, cladribine, tretinoin, arsenic trioxide) or partial responses associated with improvements in blood counts from hazardous levels to safe levels (fludarabine).

The requisite evidence supporting clinical benefit in a single-arm trial in CML may vary according to disease stage or clinical setting.

- In the *early treatment* of chronic phase CML, reports indicate that alpha interferon improves survival. For approval of a new drug in this setting, a survival benefit should be demonstrated.
- In the setting of *Chronic phase CML failing interferon*, there are three subgroups of patients.
 - Patients who are *intolerant of interferon* have few options. Durable hematologic responses may benefit patients because they are spared the symptoms associated with elevated white blood cell counts.
 - Few options exist for treating CML that is *refractory to alpha interferon* (disease progression while on interferon treatment) exist. In this setting also, durable hematologic responses may be clinical benefit.
 - However, patients with *CML resistant to alpha interferon* have a viable alternative to investigational treatment. *Resistance* refers only to the failure to achieve a hematologic or a cytogenetic response within a specified time. Patients with this subcategory of CML may sometimes still obtain hematologic responses from alpha interferon or hydroxyurea. Survival is the optimal endpoint for demonstrating benefit in these patients.
- For *accelerated phase CML*, options are limited. Patients are often uncomfortable from increasing doses of interferon and symptoms associated with high white counts

and organomegaly (enlargement of liver and spleen). Hematologic responses of sufficient duration may be considered clinical benefit.

- For *blast crisis*, options are even more limited. Survival is short (3-6 months) and patients suffer from symptoms and complications from increased numbers of blasts (immature fast-growing white blood cells) and painful enlargement of liver and spleen; complications also result from too few normal blood cells. Treatments, providing a brief remission for some patients, are attained at the cost of considerable toxicity associated with high-dose chemotherapy. Hematologic responses of sufficient duration might be considered clinical benefit. The rate and duration of response defining clinical benefit in blast crisis would be less stringent than in accelerated phase CML.

b. Surrogates for accelerated approval

Subpart H of the NDA regulations allows *accelerated approval* for serious or life-threatening diseases. For indications where the new drug appears to provide *benefit over available therapy*, accelerated approval may be granted on the basis of 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.

For this NDA, the FDA considered three surrogate endpoints *reasonably likely to predict clinical benefit*:

- Hematologic response (HR): This was a primary endpoint in trials of *accelerated phase* and *blast crisis* CML. A hematologic response requires less than 15% blasts in blood and bone marrow and requires there be no evidence of extramedullary disease. Hematologic response could be a surrogate endpoint for accelerated approval in settings where large numbers of blasts (immature, quickly growing leukemia cells) are the immediate clinical problem, settings such as *blast crisis* or *accelerated phase* CML.
- Complete hematologic response (CHR): The definition of CHR differed slightly among the trials, but required normal numbers of functional white blood cells and platelets, with no blasts. This could be a surrogate in any setting of CML.
- Major cytogenetic response (MCyR): The percent Philadelphia chromosomes (Ph+) on bone marrow karyotyping determines this endpoint. MCyR is the number of partial cytogenetic responses (defined as $\leq 35\%$ Ph+ metaphases) plus complete cytogenetic responses (0% Ph+). MCyR is a reasonable surrogate in any setting because treatments that have high rates of MCyR have been associated with improved survival

Outlined above are surrogate endpoints DODP is relying on to recommend accelerated approval of this NDA.. Note that the accelerated approval regulations require that, in addition to finding improvement in a surrogate, FDA must find that the new drug provides benefit over available therapy.

In the following sections, as we outline the efficacy findings for the three proposed indications for treating CML, we will also discuss whether the findings meet the standards necessary to support approval, either traditional approval or accelerated approval, that is:

- whether the findings constitute clinical benefit, justifying traditional approval
- whether the findings are a surrogate reasonably likely to predict clinical benefit and appear to provide benefit over available therapy, justifying accelerated approval.

2. Efficacy of imatinib in NDA studies of CML

This section describes the studies, the efficacy results, and the regulatory interpretation of those results.

a. Chronic phase CML after failure of alpha interferon, Study 110

Study description

Alpha interferon, approved by FDA for treatment of early chronic phase CML, causes cytogenetic responses (assessed in bone-marrow samples) and increases survival. Study 110 was submitted to support imatinib treatment of chronic phase CML after failure of alpha interferon. In this single-arm study, 532 patients were treated with imatinib 400 mg/day for an average of six months (16 to 320 days). This study has three subgroups, divided according to CML response to prior alpha interferon:

- Hematologic failure on interferon (152 patients)
- Cytogenetic failure on interferon (186 patients)
- Patients intolerant of interferon (194 patients)

Efficacy results

Important efficacy endpoints were cytogenetic response and complete hematologic response:

- Major cytogenetic response (MCyR) was documented in 49% (265/532) and a complete cytogenetic response (CCyR) in 30% (160/532). Median time to MCyR was 3 months. Median response duration cannot be determined yet because of short follow-up.

- Complete hematologic response (CHR) was documented in 88% (467/532). Median time to CHR was 22 days. Because of short follow-up, the median duration of CHR cannot be determined, but it must be a minimum of 6 months; more than half of entered patients (63%) were in CHR at the 6 month evaluation.

Results were similar in the three subgroups (interferon-refractory, interferon-resistant, and interferon-intolerant).

Regulatory interpretation of efficacy results

These data do not support full approval for this indication. We have no comparative data on survival, the standard endpoint for clinical benefit in chronic phase CML. We also have no dependable data on duration of CHR. Data from a randomized comparative trial will probably be needed to determine whether imatinib produces clinical benefit that merits traditional approval for this indication.

In view of the acceptable safety profile of imatinib for this indication (discussed below), these data support accelerated approval for treatment of chronic phase CML after failure of alpha-interferon. Accelerated approval is based on the surrogate endpoints MCyR and CCyR. The rates of MCyR (49%) and CCyR (30%) with imatinib treatment are at least as good as results reported with standard therapy. As discussed in detail in the FDA medical officer review (Section 12.3), almost all studies of interferon plus ara C chemotherapy in early chronic phase CML show an MCyR rate less than 20%. Furthermore, in registration trials of alpha interferon (Roferon-A®) in early chronic phase CML, the rates of MCyR were only 10% and 12%. From these data we conclude there is no available therapy likely to yield higher rates of cytogenetic response in chronic phase CML failing alpha interferon.

b. Accelerated phase CML, Study 109

Study description

During the accelerated phase of CML, disease becomes increasingly resistant to treatment. This phase is marked by the appearance of a moderate number of blasts (immature resistant leukemia cells) in the bone marrow and blood and by progressive resistance to treatment. Study 109 was a single-arm trial of imatinib treatment in 235 patients with accelerated phase CML. A third of the patients (77) received 400 mg/day and the remaining 158 patients received 600 mg/day. The median duration of treatment was about 8 months (6 to 399 days).

Efficacy results

Important efficacy endpoints were cytogenetic response and hematologic response:

- Major cytogenetic response (MCyR) was documented in 21% (50/235). Median duration of response cannot be determined yet because of short follow-up.

- Hematologic response (HR) was documented in 63% (148/235). Because of short follow-up, the median duration of HR cannot be determined. However, it is greater than 6 months because data for half of the responders were censored at or beyond 6 months. Complete hematologic response (CHR) was documented in 26% (60/235).

Regulatory interpretation of efficacy results

These data do not support full approval for this indication. Although complete hematologic response of a sufficient duration might be considered clinical benefit in this setting, further follow-up is needed to make this determination.

In view of the acceptable the safety profile (discussed below), these data support accelerated approval for imatinib treatment of accelerated phase CML. Accelerated approval is based on the surrogate endpoints hematologic response (HR) and major cytogenetic response (MCyR). The rates of HR (63%) and MCyR (21%) with imatinib treatment are at least as good as any results reported in the literature even with highly toxic treatments. As discussed in section 12.2 of the medical officer review, in two studies evaluating toxic multi-agent chemotherapy, the HR rates were 25% and 52% and the rate of MCyR was 8% and 8.5%. Imatinib provides an advantage over available therapy for accelerated phase CML by achieving high rates of HR and McyR that are at least comparable and possibly better than achieved with available therapy, and it is less toxic.

c. Blast Crisis CML, Study 102

Study description

CML terminates in blast crisis, a rapidly fatal condition similar to acute leukemia where blasts replace the bone marrow and patients die from bone marrow failure. Few treatment options exist for blast crisis. High dose chemotherapy is sometimes given for patients who can tolerate the associated toxicity. Response rates are low and benefit is transient. Study 102 is a single-arm study that evaluated imatinib treatment in 260 patients with blast crisis. Although the trial started with a dose of 400 mg/day, after a protocol amendment, 223 of the 260 patients received a starting dose of 600 mg/day. At this dose, 88 patients have been treated for at least 3 months and 35 patients have been treated for at least 6 months.

Efficacy results

The primary endpoint was hematologic response. Hematologic response (HR) was documented in 26% (68/235). Data do not yet allow a reliable estimate of median duration of response. Complete hematologic response (CHR) was documented in 4% (11/276).

Cytogenetic responses were also observed. Major cytogenetic response (MCyR) was documented in 14% (35/235).

Regulatory interpretation of efficacy results

We do not believe these data are mature enough to support full approval, although this could change with follow-up and with determination of response duration. In the setting of blast crisis, where the only viable treatment option is high dose chemotherapy, durable hematologic response might be considered clinical benefit and therefore support traditional approval.

Given the acceptable safety profile for this indication (discussed below), these data support accelerated approval for imatinib treatment of CML in blast crisis. Accelerated approval is based on the surrogate endpoint hematologic response (HR). The rate of HR (26%) with imatinib treatment is comparable to results reported in the literature with highly toxic treatments. As discussed in section 12.1 of the medical officer review, in a large study of patients with CML blast crisis treated with high-dose chemotherapy (acute leukemia regimens), the HR rate was 23% and the median survival was 4.5 months. Imatinib provides an advantage over available therapy for accelerated phase CML by achieving comparable HR response rates with less toxicity. Toxicity is an important issue in the setting of blast crisis because survival is short and palliation is the goal of therapy.

C. Safety

1. Adequacy of testing

The following table gives the exposure to imatinib in the NDA safety database. The numbers in parentheses represent the number of patients who have been followed on treatment for at least 6 months.

Number of patients and starting dose of imatinib

	<u>400 mg</u>	<u>600 mg</u>
Study 102 (BC)	37 (21)*	223 (35)
Study 109 (AP)	77 (49)	158 (125)
<u>Study 110 (CP)</u>	<u>532 (459)</u>	
Total	646 (529)	381 (160)

*# patients followed at least 6 months

381 patients have been treated at a starting dose of 600 mg/day and 160 patients have been treated for at least 6 months. 646 patients have been treated at a starting dose of 600 mg/day and 529 have been followed for at least 6 months. Given the poor prognosis of the patients and the encouraging early evidence of efficacy described above, this follow-up is adequate to support accelerated approval for the proposed indications. However, safety data from ongoing trials should be promptly analyzed and reported to FDA so that the imatinib package insert can be quickly updated.

2. Common side effects

GI complaints were common, with nausea or vomiting occurring in 60-70% and diarrhea in 30-50%. Severe GI adverse events were reported in 3-5% of patients at 600 mg/m² and 1-2% at 400 mg/m². Musculoskeletal complaints, such as muscle cramps (25-50%), myalgias (17-18%), and arthralgias were also common (21-25%). Severe musculoskeletal AEs were reported in 1-5% of patients. Edema was also common as discussed in the next section.

3. Serious side effects

Severe adverse events (SAEs) were reported in 36% of patients in the safety database, although investigators attributed these events to drug in 10%. In Study 110, where the dose was lower (400mg) and disease less advanced (CML CP), the rate of reported SAEs was lower (18%). The following sections of this document discuss the side effects of most concern, the syndrome of fluid retention and edema, hepatotoxicity, and myelosuppression.

a. Fluid retention and edema

Fluid retention and edema occurred commonly. The incidence of these events is tabulated below (the incidence of grade 3 or 4 toxicity is in parentheses). Reported toxicity grades use the NCI Common Toxicity Criteria (CTC).

Study (Disease)	<u>102 (BC)</u>	<u>109 (AP)</u>	<u>110 (CP)</u>
Edema	63% (5%)*	66% (4%)	51% (1%)
Wt. gain/fluid retention	15% (5%)	15% (4%)	9% (2%)

*the incidence of grade 3-4 toxicity is in parentheses

Periorbital edema and extremity edema were the most common complaints. CTC grade 3-4 weight gain and fluid retention, consisting of pleural effusions, ascites, or pericardial effusions, occurred in 4-5% of patients with CML-BC or CML-AP and in 2% in CML-CP. These symptoms were treated with diuretics in up to a third of all patients. Bilateral macular edema was reported in a patient in Study 109-AP who had a history of ocular hypertension.

The incidence of edema was clearly dose-related; not only was the incidence higher in the studies where most patients received the higher 600 mg dose (Study 102 [BC] and Study 109 [AP]), the incidence of edema was about 20% higher within each of these studies for patients who received 600 mg versus 400 mg. In the overall safety population there were 37 patients (3.0%) with a severe adverse event (SAE) reported as fluid retention. Fifteen of these patients had a history of ischemic heart disease or prior pulmonary edema.

The actual number of such events caused by imatinib treatment is difficult to ascertain in these studies. Very ill patients with blast crisis or accelerated phase CML often have severe events from infection or from progression of disease where the exact etiology may be unclear. In study 102 (BC), deaths occurred in association with severe fluid retention AEs in 3.4% (9/260). The investigator attributed death to drug-associated fluid retention in only one case. In four cases patients died with respiratory distress and fluid overload;

two patients had pleural effusions and ascites but also had progression of disease, and two patients had acute respiratory distress syndrome that might have been from infection. If we attribute these five deaths to drug, the incidence of fluid overload and death in CML BC is 2% (4/260).

b. Hepatotoxicity

Liver toxicity was predicted by animal studies, primarily by dog studies showing mild focal necrosis of hepatocytes and bile duct cells. The reversibility of hepatotoxicity in dogs was not clear because bile duct abnormalities were even more severe after 4 weeks off drug. In clinical studies, elevated liver function tests were reported as serious events in 35 patients (2.8%) in the overall database. In 11 of these patients both bilirubin and transaminases were elevated. One death was thought due to liver failure. Six patients discontinued imatinib because of these events. Reversible elevation of bilirubin and transaminases occurred after an overdose of 1200 mg given for 8 days.

In the following paragraphs, clinical hepatic toxicities are discussed for each of the three studies. Liver test abnormalities were grouped according to NCI CTC criteria:

	<u>Grade 1-2</u>	<u>Grade 3-4</u>
Transaminases and Alkaline phosphatase	>ULN*	>5 X ULN
Bilirubin	>ULN	>3.0 X ULN

*ULN = upper limit of normal

In Study 102 (BC) the incidence of grade 3-4 abnormalities of liver function tests was 12% (30/260). In all but 4 patients (1.5%) FDA reviewers determined that complications of CML may have caused the abnormality. In this study, elevations of transaminases in combination with bilirubin were seen in 4% (11/260). Many of these cases were pre-terminal findings associated with CML progression and multiorgan failure.

In Study 109 (AP) the incidence of grade 3-4 abnormalities of liver function tests was 4% (10/235). In most cases tests normalized, and imatinib was subsequently tolerated at a lower dose. The following two cases are notable:

- Budd Chiari syndrome (hepatic vein thrombosis) was reported in one patient on day 38. Imatinib was discontinued and tests normalized.
- A patient taking acetaminophen died from liver failure after 7 days of imatinib at a dose of 600 mg/day. For one month prior to study entry the patient took acetaminophen 3-3.5 gm/day for fever and also took fluconazole for oral candidiasis. At study entry, liver transaminases and alkaline phosphatase were mildly elevated. Right upper quadrant pain led to detection of severely elevated liver function tests on day 7. Imatinib was discontinued, but the patient died of hepatic failure on day 12.

In Study 110 (CP), 532 patients were given imatinib 400 mg/d. The incidence of liver function test or hepatotoxicity SAEs was 1.3% (7/532). In two cases, imatinib was discontinued. In the others, tests normalized, and imatinib was restarted without recurrence of the liver test abnormalities.

The above preclinical and clinical findings suggest that hepatotoxicity is a serious concern. Labeling should recommend careful monitoring of liver function tests.

c. Myelosuppression (cytopenias)

Doses were adjusted according to expected hematologic cytopenias (neutropenia and thrombocytopenia). The following table shows the incidence of Grade 3-4 neutropenia and thrombocytopenia.

Incidence of Grade 3-4 neutropenia or thrombocytopenia*				
Study (CML phase)	102 (BC)	109 (AP)	110 (CP)	
Gr. 3-4 Neutropenia	62%	58%	33%	
Gr. 3-4 Thrombocytopenia	58%	42%	17%	

*Granulocyte count < 1.0X10⁹/l or platelet count < 50X1.0X10⁹/l

Grade 3-4 neutropenia and thrombocytopenia were more common in patients with blast crisis and accelerated phase CML than chronic phase CML failing interferon. Median onset of neutropenia was earlier for blast crisis (2 weeks) than for the earlier phases of CML (5-8 weeks). The median duration of neutropenia was 2-4 weeks.

4. Dosing

The recommended dose and schedule (400 mg/d for CML CP failing interferon and 600 mg/d for CML AP and for CML BC) and the recommendations for dose modification are reasonable. As discussed below, this conclusion is based on dose-response, dose-toxicity, and pharmacokinetic data.

Evidence for a relationship between dose and response come from clinical data on sequential groups of patients treated with two doses (400 mg/d and 600 mg/d) in two trials (102 [BC] and 109 [AP]). Studies in all indications were started at an initial dose of 400 mg/day. After phase I data demonstrated the safety of the 600 mg dose, this became the starting dose for new patients accrued to studies 102 (BC) and 109 (AP). Dose escalation was allowed. Doses in all trials were decreased according to toxicity-based criteria outlined in the protocol and in the proposed labeling. Despite escalating and decreasing doses in some patients, the median dose delivered per day was similar to the starting dose in all studies.

The following dose-response data suggest relationship between dose and CML response at the doses of 400 mg and 600 mg in treatment of CML BC and CML AP. We have no data on dose-response in CML CP, because Study 110 used only the 400 mg dose.

Study	Hematatologic Response (HR)		Major Cytogenetic Response (MCyR)	
	400 mg	600 mg	400 mg	600 mg
102 (BC)	11% (4/37)	29% (64/223)	8% (3/37)	14% (32/223)
109 (AP)	63% (48/72)	63% (44/158)	16% (12/72)	24% (38/158)

In these nonrandomized exploratory analyses, results are more favorable in the 600 mg arm for hematologic response in Study 102 (BC) and for major cytogenetic response in both studies. The sponsor's analysis of time to progression in the 109 (AP) study also suggests a superior result for the 600 mg dose in AP.

Dose-toxicity data were discussed previously. The incidence of edema was increased at the 600 mg dose in both the 102 (BC) and 109 (AP) studies.

FDA population pharmacokinetic analyses suggest that fixed dosing, as proposed by Novartis, is acceptable. However, variation in imatinib plasma clearance among patients was substantial (40% coefficient of variation). The findings of a wide variation in clearance coupled with the finding of a relationship between dose and toxicity call for future research to decrease differences in inter-patient variation in imatinib blood levels. Possible approaches are adjusting dose based on imatinib blood levels or adjusting dose based on individual baseline patient characteristics.

In summary, data suggest that 600 mg/day may be more effective but also may be more toxic than 400 mg/day in patients with CML-AP and CML-BC, and we have no data to assess these findings in CML-CP. The doses proposed by Novartis seem appropriate at this time. Future research is needed to further define the optimal dose for each CML phase and to provide better dose-selection based on individual patient characteristics.

5. Drug-drug interactions

Significant drug-drug interactions are expected with imatinib. Imatinib is metabolized by, and also inhibits, hepatic P450 isoenzyme CYP3A4. Drugs that inhibit CYP3A4 will increase imatinib concentrations and may increase toxicity. A patient suffered an intracerebral hemorrhage possibly related to inhibition of hepatic excretion of warfarin.

Drugs that induce activity of CYP3A4 will decrease imatinib levels and may decrease efficacy. A patient taking dilantin (an inducer of CYP3A4) had markedly decreased blood levels of imatinib associated with a lack of efficacy in CML.

Appropriate precautions about potential drug interactions will be included in the package insert including specific precautions about warfarin.

6. Special populations

This section discusses imatinib use in special populations according to age, gender, race, pregnancy, childhood, and impaired organ function.

The median age of the 1027 patients in the safety database was 55 years; 22% were 60-70 and 11% were older than 70 years of age. The safety data suggested a slight increase in frequency of grade 1-2 edema in patients over 65 years of age. In addition, the FDA population pharmacokinetic analysis suggested that increasing age was a risk factor for grade 3 edema at higher blood levels of imatinib. These data will be described in the drug labeling.

Women comprised 45% of the patients studied. There was a slight increase in grade 1-2 periorbital edema, headache, and fatigue in women.

No statement can be made regarding the relationship of safety or efficacy to race or ethnicity. The number patients treated, according to race, is listed below:

Caucasians	894 (87%)
Blacks	63 (6%)
Asian	15 (1.5%)
Other	55 (5%)

There are two few patients in these subgroups for meaningful subgroup comparisons of safety or efficacy, especially considering there are 3 indications and 2 doses to consider.

Imatinib was teratogenic in animals, therefore, patients taking imatinib should avoid pregnancy. Two patients became pregnant during studies and had not delivered at the time of NDA submission. Information on the outcome of these pregnancies should be included promptly in future labeling.

Only 6 pediatric patients have been studied in phase I trials. This NDA is not subject to the Pediatric Rule (which requires pediatric studies to be performed in some circumstances) because imatinib is an *Orphan Drug*. A pediatric written request, which outlines pediatric studies that would grant additional marketing exclusivity, has been sent to Novartis. In addition Novartis agreed to perform pediatric studies as a phase IV commitment.

The final special population we consider is patients with impaired organ function. Imatinib is excreted primarily by the liver. Novartis has committed to perform phase IV studies in patients with hepatic impairment.

7. Safety concerns from animal studies

Given the relatively short follow-up of patients in the safety database, it is important to consider toxicities caused by imatinib in animals. Hepatic toxicity, renal toxicity, and immunosuppression are animal findings of particular concern. The animal hepatic findings were discussed in previous sections of this document. Immunosuppression and renal toxicity are discussed below:

- **Potential immunosuppression.** In a 39-week monkey study, treatment with imatinib affected the immune reaction to malaria. Asymptomatic malaria is normally endemic in monkeys. Recrudescence malaria was observed in monkeys treated with imatinib. Novartis suggests that imatinib inhibits PDGF (platelet derived growth factor) leading to a decrease in production of nitric oxide (NO). NO is thought play an important role in killing parasites.

In addition to concern raised by the monkey studies, we are concerned by the lympholytic effect of imatinib. Treatment with imatinib causes lymphopenia in animals and humans. Given the relatively short follow-up in the clinical database, physicians should be to be alerted that an increased rate of opportunistic infections could occur with chronic imatinib treatment.

- **Renal toxicity.** The renal findings observed in animals are of uncertain significance. Histologic changes, without associated changes in serum chemistries, were seen in two studies. In one rat study hyperplasia of transitional epithelium was observed. In a monkey study, there was focal mineralization and dilatation of renal tubules and tubular nephrosis. The clinical significance of these findings is not clear, but given the short follow-up in the clinical database, these findings should be included in the package insert.

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ON ORIGINAL**

III. Conclusions

FDA's Division of Oncology Drug Product (DODP) recommends accelerated approval of Gleevec™ (imatinib mesylate capsules) for the proposed indications in chronic myeloid leukemia (CML). We recommend the following wording for the INDICATIONS AND USAGE section of the package insert:

"GLEEVEC is indicated for 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 (see Clinical Studies section). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival."

Follow-up in patients treated with imatinib is relatively short but is adequate for the recommended indications. Prompt evaluation and reporting of new safety information will be important.

Phase IV commitments by Novartis are listed in Section I of this document.

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ON ORIGINAL

Medical Officer Review of NDA 21-335

Drug Name: Gleevec™ Imatinib mesylate capsules

Applicant: Novartis

Date Submitted: February 27, 2001

Date Received: February 28, 2001

Date of Review: April 20, 2001

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NDA 21-335 is comprised of three uncontrolled efficacy and safety studies for the treatment of patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in blast crisis (study 0102), accelerated phase (study 0109) and chronic phase, resistant, refractory or intolerant to interferon therapy (study 0110). Small numbers of patients with other Ph+ leukemias were also studied. A total of 1,234 patients were enrolled in these trials. Data from a multiple dose tolerability/dose finding study is also included. Study synopses are provided in Section 11.0.

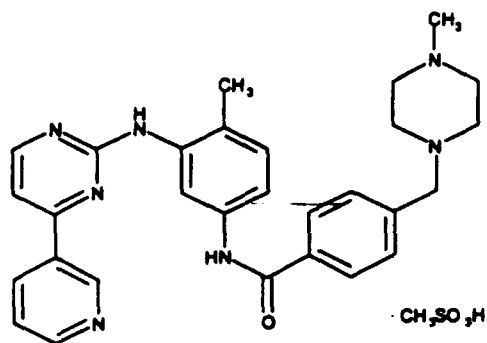
1.0 General Information

STI571 (formerly CGP 57148B) is a protein-tyrosine kinase inhibitor that shows selectivity for the Abl protein-tyrosine kinase at the *in vitro*, cellular and *in vivo* level. The compound blocked proliferation of Bcr-Abl-expressing chronic myelocytic leukemia (CML) and acute lymphocytic leukemia (ALL) cell lines and induced apoptosis in both cell lines and fresh leukemic cells from Philadelphia (Ph) chromosome positive CML and ALL patients. In animal models, the compound shows potent anti-tumor activity against Bcr-Abl and v-Abl expressing cells at tolerated doses. In addition, STI571 is a potent inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events.

The phase I (03 001) study of STI571 failed to demonstrate a MTD up until a dosage of 1000 mg/d. It did however provide evidence of hematologic and cytogenetic response in the various CML disease phases at doses in excess of 300 - 400 mg/d. These responses appeared mostly within the first month of treatment.

1.1 Description and Characteristics

STI571 is designated chemically as 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate. Its molecular formula is $C_{29}H_{31}N_7O \cdot CH_4SO_3$ and its structural formula is:



STI571 is a white to off-white to brownish or yellowish tinged crystalline powder. STI571 is very soluble in water and soluble in aqueous buffers \leq pH 5.5. Inactive ingredients include colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose. Capsule shell: Gelatin, Iron oxide, red (E172); Iron oxide, yellow (E172); Titanium dioxide (E171).

1.2 Pharmacokinetics

The pharmacokinetics of STI571 have been evaluated in 591 patients and 33 healthy subjects over a dosage range of 25 to 1000 mg.

1.2.1 ADME

Absorption

Mean absolute bioavailability for the capsule formulation is 98%. The coefficient of variation for plasma STI571 AUC is in the range of 40-60% after an oral dose. When given with a high fat meal the rate of absorption of STI571 was minimally reduced (11% decrease in C_{max} and prolongation of t_{max} by 1.5h), with a small reduction in AUC (7.4%) compared to fasting conditions.

Distribution

At clinically relevant concentrations of STI571, binding to plasma proteins is approximately 95% on the basis of *in vitro* experiments, mostly to albumin and α_1 -acid glycoprotein, with little binding to lipoprotein.

Metabolism

The main circulating metabolite in humans is the N-demethylated piperazine derivative, which shows similar *in vitro* potency as the parent. The plasma AUC for this metabolite was found to be only of the AUC for STI571.

Elimination

Based on the recovery of compound(s) after an oral ¹⁴C-labelled dose of STI571, approximately 81% of the dose was eliminated within 7 days in feces (68% of dose) and urine (13% of dose). Unchanged STI571 accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

1.2.2 Plasma pharmacokinetics

Following oral administration in healthy volunteers, the t_{1/2} was approximately 18 hours. Plasma pharmacokinetic profiles were analyzed in CML patients on Day 1 and on either Day 7 or 28, by which time plasma concentrations had reached steady state. The increase in mean STI571 AUC with increasing dose was linear and dose proportional in the range 25-1000 mg after oral administration. There was no change in the kinetics of STI571 on repeated dosing, and accumulation is 1.5-2.5 fold at steady state when STI571 is dosed once daily.

1.2.3 Population pharmacokinetics

The effect of body weight on the clearance of STI571 is such that for a patient weighing 50 kg the mean clearance is expected to be 8.5 L/h, while 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. There is no effect of gender on the kinetics of STI571.

Organ function impairment

STI571 and its metabolites are not excreted via the kidney to a significant extent. Exposure to STI571 may be expected to increase if liver function is impaired.

Pharmacokinetic-pharmacodynamic relationship

In the phase I study a positive dose response of hematologic effects was established over the dose range 25 mg to 1000 mg. Normalization of WBCs to $<10 \times 10^9/l$ by day 28, was observed at daily doses 400 mg.

1.2.4 Special Populations

Pediatric: There are no pharmacokinetic data in pediatric patients.

Geriatric: Based on population PK analysis, there was a small effect of age on the volume of distribution (12% increase in patients > 65 years old). This change is not thought to be clinically significant.

Hepatic Insufficiency: No clinical studies were conducted with STI571 in patients with elevated transaminases and bilirubin (defined as more than 3 times the upper limit of the normal range, or 5 times in the presence of leukemic involvement of the liver) at baseline. As STI571 is metabolized by the liver it should be used with caution in patients with liver impairment.

Renal Insufficiency: No clinical studies were conducted with STI571 in patients with decreased renal function (serum creatinine concentration more than 2 times the upper limit of normal). STI571 and its metabolites are not excreted via the kidney to a significant extent.

1.2.5 Drug-Drug Interactions

There was a significant increase in exposure to STI571 (mean C_{max} and AUC increased by 26% and 40%, respectively) in healthy subjects when STI571 was co-administered with a single dose of ketoconazole (a cytochrome P450 isoenzyme CYP3A4 inhibitor). STI571 increased the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) by 2- and 3.5- fold, respectively, indicating an inhibition of the CYP3A4 by STI571. Inhibition of CYP3A4 at clinically relevant doses of STI571 may increase the exposure to co-medications, which are

substrates of CYP3A4. Because warfarin is metabolized through the CYP450 system patients who require anticoagulation will receive low-molecular weight or standard heparin. Mini-dose coumadin for prophylaxis of central venous catheter prophylaxis may be used.

1.3 Chronic myeloid leukemia (CML)

Chronic myeloid leukemia (CML) is a hematologic neoplasm associated with a specific chromosomal translocation known as the Philadelphia (Ph) chromosome. The Ph chromosome is detected in 95% of patients with CML and in 20% of adults with acute lymphocytic leukemia (ALL). The molecular consequence of the translocation is the fusion of the Abl proto-oncogene to the BCR gene resulting in the production of an activated form of the Abl protein-tyrosine kinase. The Bcr-Abl protein is capable of inducing leukemia in mice, implicating the protein as the cause of these diseases. The tyrosine kinase activity of the Bcr-Abl protein is essential to its transforming ability.

CML progresses through three clinical phases of increasing refractoriness to therapy: chronic phase (median duration 4-5 years), accelerated phase (median duration about one year), and blast crisis (median duration 3-6 months). During the chronic phase of the disease, myeloid cells containing Bcr-Abl retain the capacity to differentiate normally. Accelerated phase is an intermediate stage where patients show signs of disease progression. Eventually, there is progressive loss of the capacity for terminal differentiation resulting in disease progression to blast crisis (effectively an acute leukemia) which can be either of myeloid or lymphoid morphology.

CML patients in myeloid blast crisis pose a major management challenge. Although a number of regimens have been studied including induction therapies for acute myeloid leukemia (AML) and hematopoietic stem cell transplantation, there is no standard therapy for these patients. Long-term survival rates of 5-10% have been reported following allogeneic transplantation. Poor responses have been reported for AML-like induction regimes as first line therapy.

2.0 Regulatory History

2.1 Sponsor-FDA Meeting Minutes December 7, 1999

Issues to be discussed and sponsor's questions.

The proposed chronic phase CML trial is a phase II, non-randomized evaluation of STI571 an inhibitor of the protein-tyrosine kinase associated with Bcr-Abl in CML patients who are refractory to or are intolerant of IFN α . The major issues in this trial are 1) that it is non-randomized, 2) that it uses definitions of IFN refractory disease that are not universally accepted, and 3) that it will provide little useful information regarding time-to-event endpoints.

The sponsor's stated reason for the non-randomized design is because of the poor activity of hydroxyurea as either first- (<5% major cytogenetic responses) or second-line therapy. In

addition, the ongoing Phase I study with STI571, doses of 300 to 600 mg administered daily have induced CHR's in 31 of 31 patients (100%). With only limited follow-up of the 22 patients treated at doses of 300 to 500 mg of STI571, major and minor cytogenetic responses have already been documented in 2 (9%) and 9 (41%) patients, respectively.

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

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

Sponsor's Questions

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

FDA Response:

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

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

FDA Response: No.

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

FDA Response: No.

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

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

FDA Response: No

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

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

FDA Response:

See our response to 1a.

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

FDA Response:

No

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

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

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

FDA Response:

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

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

FDA Response:

See above

Additional FDA Comments:

Clinical Pharmacology and Biopharmaceutics

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

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

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

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

is at the convenience of the patient. Please clarify.

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

Currently the sponsor intends to sample out to possibly one $t_{1/2}$ (24 hours). STI571 has a $t_{1/2}$ of 10 to 23 hours making the sampling regimen inadequate for a full profile assessment (out to 3 $t_{1/2}$).

2.2 Sponsor-FDA Meeting Minutes May 3, 2000

Topics for Discussion

This briefing book outlines a registration program that will consist of the following three sequential submissions for patients with chronic myelogenous leukemia (CML):

The initial registration will include the submission of data from three non-randomized phase II trials in different CML subpopulations:

myeloid blast crisis – Protocol 0102

accelerated phase – Protocol 0109

chronic phase patients hematologically refractory or resistant to interferon – Protocol 0110

A supplemental application will include the submission of the results of an analysis performed at 1 year on the randomized phase III trial in newly diagnosed chronic phase CML (Protocol 0106). These results will focus on equivalence of the STI571 arm in terms of rate of complete hematologic response and superiority of the STI571 arm in terms of quality of life.

Submission of the results of the analysis performed at 5 years on the randomized phase III trial in early chronic phase CML (Protocol 0106) will provide confirmatory evidence of activity. These results will focus on superiority of the STI571 arm in terms of time to treatment failure.

Regarding the initial registration in patients with advanced CML:

We propose to register STI571 according to the provisions described in 21 CFR 314, Subpart H - Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. We believe that STI571 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). A randomized controlled trial in patients with chronic stage CML will subsequently provide confirmatory evidence of activity.

Are the three subpopulations adequately defined (Sections 3.2, 3.3, 3.4)?

FDA Response:

Patients with blast crisis, accelerated phase, and interferon refractory chronic phase are adequately defined.

Patients with interferon hematologic or cytogenetic resistant chronic CML are not appropriate study populations. These are unique, sponsor defined, study populations. Other investigators might consider these individuals to have stable disease and would continue interferon treatment.

Do you agree that the primary efficacy endpoint of response rate (complete hematologic response in Protocols 0102 and 0109 or complete plus major cytogenetic response in Protocol 0110) is an appropriate surrogate endpoint that is reasonably likely to predict Clinical benefit in the proposed populations?

FDA Response:

For blast crisis and accelerated phase CML CHR is an adequate endpoint. There are other drugs that produce CHR's that are available for use in these conditions. That is the reason the FDA has recommended RCTs at the prior FDA/Novartis meeting (6-15-99). However, if the Phase II CHR rates are very good and are reasonably durable, it may be possible to conclude that STI 571 is better than available therapy without RCTs.

For chronic phase CML (protocol 0110) it is still controversial as to whether either CHR or complete plus major cytogenetic response are adequate surrogate endpoints for clinical benefit in the proposed patient populations. Sponsor would have to provide convincing evidence regarding this issue.

The eligibility criteria for study 0110 regarding hematologic resistance and cytogenetic resistance are not acceptable.

For responding patients, would a median duration of response (Protocol 0110) or time to treatment failure (Protocols 0102 and 0109) of at least 6 months be sufficient to demonstrate durability?

FDA Response:

The FDA does not agree with the proposed criteria for time to treatment failure. See FDA answer to Question 2 b below. Therefore the time to treatment failure part of the question is not answerable.

For study 0102 (Blast crisis CML) a ≥ 6 months median duration of CHR would be sufficient durability. The new proposal for ≥ 3 months median duration of CHR is not acceptable.

For study 0109 (Accelerated phase CML) a 6 months median duration of CHR would probably not be sufficient durability. Median survival of accelerated phase patients, based on MDACC data, varies widely (from 7 months to ~ 50 months). Depending on patient mix a considerably longer median duration of CHR might be expected.

For study 0110 (Chronic Phase CML INF refractory/resistant) a median duration of complete or major cytogenetic response of at least 6 months would not be sufficient to demonstrate durability.

For study 0110 we suggest the following primary efficacy endpoints, but these would be difficult to assess without a RCT.

Time to accelerated phase or blast crisis or
Time to death.

Does the proposed Phase II program support an initial registration in patients with the defined stages of CML?

FDA Response:

For acute blast crisis and accelerated phase CML, possibly depending upon study results.

For Chronic Phase CML interferon refractory probably not.

See answer to questions 1a, 1b and 1c.

Regarding subsequent registration in newly diagnosed chronic phase CML

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

FDA Response: No

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

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

It is highly unlikely that accelerated approval for newly diagnosed CML could be given based solely on better QOL as measured by the proposed FACT-BRM quality of life instrument. There would need to be a demonstration of a strongly favorable effect on other QOL measures such as drug toxicity and disease related symptoms.

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

FDA Response: No.

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

Failure to achieve CHR at 6 months and failure to achieve a cytogenetic response at 24 months are not shown to be adequate surrogates for survival or other Clinical benefit.

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

Time to onset of accelerated phase or blast crisis or

Time to Death

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

As previously discussed accrual to this phase III study should be complete before phase II studies are submitted for accelerated approval.

3. Philadelphia chromosome positive leukemias in children

Study 0103 (Section 4.2) is a dose-finding study in children with refractory/relapsed Ph+ leukemias designed to obtain pharmacokinetic and safety data. Preliminary evidence of efficacy will also be obtained. As described in our January 21, 2000 (serial no. 032) Proposed Pediatric Study Request, a formal efficacy trial in children is not planned as efficacy in this patient group can be extrapolated from the data obtained in adults.

It is anticipated that a clinical trial report for study 0103 will be submitted as a labeling supplement following the initial registration. Do you agree that preliminary evidence of efficacy, together with dosing, pharmacokinetic, and safety data in pediatric patients will be sufficient to expand the labeling to include the treatment of children with Ph+ leukemias?

FDA Response: No

A phase II efficacy study must be done in an appropriate pediatric population.

Clinical Pharmacology and Biopharmaceutics review comments:

Additional Comments generated from the meeting package:

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

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

Additional Statistical Comments:

For protocol 106: The log-rank test should be the primary analysis for the time to event endpoints. The Cox regression analyses should be considered as secondary analyses.

For protocol 106: A sample size of 850 will account for a 17% dropout rate (not 20%). A sample size of 880 patients (704/0.8) will account for a 20% dropout rate.

Please clarify the purpose for the interim analyses on CHR rate and QoL endpoints. If the purpose of these analyses is to make a claim, the probability of a Type I error in the final analysis should be adjusted.

The sponsor did not respond to the first statistical comment (dated 8-27-99) for protocol 109. In that submitted protocol the sponsor stated the following, "Depending on efficacy results and rate of enrollment, the total number of patients recruited per disease group may be expanded." The

sponsor should clarify how they intend to use efficacy results and rate of enrolment to expand the total number of patients per disease group.

2.3 Sponsor-FDA Meeting Minutes August 31, 2000

Proposed Indication:

Primary Endpoint –

FDA:

Time to Treatment Failure (TTF) is not accepted as an endpoint for the following reasons:

Intolerance to treatment (inability to take the drug) cannot be an efficacy endpoint.

CHR (complete hematologic response) is not a compelling endpoint [responder vs. non-responder argument, not a surrogate for survival in most European randomized trial reports (see attachment 1), capacity to respond may be a good prognostic feature.

McyR is not a compelling endpoint (No data to support McyR as a surrogate endpoint for survival, similar arguments as for CHR, may influence tail of survival curve but not median survival)

Time to Progression (TTP) is recommended surrogate endpoint and suggestions include:

Loss of CHR

Loss of cytogenetic response

Inability to maintain peripheral blood counts (needs to be defined)

Increasing organomegaly

Accelerated phase CML

Blast crisis

Death from CML

Novartis Response: Concurs with the Agency's recommendation to substitute TTP (FDA definition) for TTF as the primary study endpoint.

Non-inferiority versus Superiority Statistical Analysis

FDA and Novartis discussed the effect of crossovers. Using TTP as the primary endpoint there will be fewer crossovers overall and much fewer early crossovers. Therefore, Novartis will design the trial to demonstrate superiority.

Novartis Response: Protocol will be amended to be a superiority trial.

Treatment Intolerance

FDA: Patients intolerant of study treatment will be censored at the time they discontinue treatment. Subsequent treatment can be at the investigator's discretion.

Novartis Response: Concurs with the Agency's recommendation.

NDA 21-335 STI571

Food Effect

FDA : Clinical Pharmacology and Biopharmaceutics Comments

We remind you of:

All the Clinical Pharmacology and Biopharmaceutics issues previously discussed that should be addressed regarding the development of STI 571.

The recent communication in which we asked you to provide the raw data and summary for the food effect study performed.

Submitting the data from the preliminary human PK results that indicates that STI 571 is rapidly absorbed when the drug is administered 2 hours after breakfast.

Submitting the solubility data that indicates that STI 571 is highly soluble in acid but has low solubility at a low pH 7.4

Novartis Response: Data from food effect study will be submitted in the near future.

ACTION ITEMS:

1. Novartis will submit an amended protocol mid-October.

Novartis will submit an amended statistical analysis plan to change to a superiority trial.

Novartis will assess the data on MCyR at 12 months and may request another meeting to discuss whether this as an acceptable surrogate endpoint for accelerated approval.

The informed consent currently being used will be reviewed and revised, as appropriate. Patients already on study may have to be re-consented.

2.4 Sponsor-FDA Meeting Minutes September 20, 2000

Clinical and Statistical

Data presentation in key efficacy trial reports

Novartis has outlined in sections 3.3.1, 3.3.2 and Appendix 5 our intended presentation of efficacy and safety data for the key efficacy trials, 0102, 0109, 0110.

Does the Division concur with the proposals for the efficacy analysis including the definitions of analysis populations (Intent-To-Treat and Per Protocol) for studies 0102, 0109, 0110?

FDA

a. The primary efficacy analysis should be on the ITT population.

Cytogenetic response requires a second confirmatory marrow performed at least 1 month after the initial marrow. If fewer than 20 metaphases are counted there must be a subsequent cytogenetic examination to confirm Ph+ status. If a confirmatory marrow is not done the fewer than 20 metaphase marrow will not be used as an indicator of cytogenetic response.

Loss of CHR may be based on a single examination.

For any category of response loss of that response will be based on a single determination.

Does the Division concur with the proposal to base the primary analysis on the Per Protocol population for studies 0102, 0109, 0110?

FDA See above.

Does the Division concur with the proposals for the safety analysis for studies 0102, 0109, 0110?

FDA

It is not clear whether all adverse events, grouped by body system; will be reported or whether only serious adverse events will be listed. The agency prefers both listings.

Composition / Presentation of Integrated Summaries

Integrated efficacy summary (ISE): Each of the three pivotal trials evaluates the activity of STI571 in a different subset of the advanced CML patient population, which clearly differ in terms of prognostic factors and expected response to treatment. Additionally, the primary efficacy variable is different in study 0110 (cytogenetic response) and studies 0102 and 0109 (hematologic response). As a result, pooling of key efficacy data from these studies would not be meaningful. It would also not be appropriate to pool efficacy data between the corresponding phase I and phase II trials because the phase I trial was not designed to evaluate efficacy and patients have been treated with varying doses of STI571. Therefore, we propose to present in the ISE (NDA Section 8) a discussion of the results of the individual phase II studies, including a side-by-side comparison of the key results across studies. Do you concur with this approach to the presentation of efficacy data across the studies?

FDA Yes

Integrated Safety Summary (ISS): It becomes apparent from an examination of emerging data that the safety profile of STI571 is likely to be different in patients with accelerated phase or blast crisis as compared to patients in chronic phase CML. In addition, the dose of STI571 used in study 0110 (400 mg) is different from the dose used in studies 0102 and 0109 (600 mg). In the phase I study, 03 001, only a small number of patients have been treated with the doses of 400 and 600 mg used in the phase II studies. For these reasons, we propose to present the safety data from the complete studies (03 001, 0102, 0109, 0110) in the ISS with a summary of findings, keeping them within the context of the individual studies. A side-by-side presentation of drug-related adverse events will be provided for the pivotal phase II trials. Do you concur?

FDA

We would like to see side-by-side summaries of all patients who received STI571 400 mg, STI571 600 mg, and STI571 at doses >600 mg. If you wish to provide additional summaries, by stage of disease, that will be acceptable.

For ongoing STI571 clinical trials, the ISS will include Serious Adverse Events for all subjects on study through July 31, 2000. Events occurring after this date will be included in the 120-day safety update. Is this cut-off date acceptable for an expected filing in January, 2001?

FDA Yes

Please advise us as to the suitability of our ISS tables to facilitate your review. (Section 3.3.2, Appendix 5)

FDA See question 10

The composition of Section 10 (statistical section) of the NDA is largely a duplication of information contained in Section 8 (Clinical section) of the NDA. We propose to submit in Section 10 identical copies of the relevant NDA volumes from Section 8, however, they would be provided in the color-coded covers for the statistical section. These volumes would bear the same

volume and page numbers as well as the original section numbering from Section 8. Is this proposal acceptable?

FDA

Yes from the Clinical perspective. See statistical comments.

Case Report Tabulations (CRTs)

14. Do you concur with our presentation of CRTs as described in Section 3.3.3 of this document to satisfy the requirements of 21 CFR 314.50(f)(1)?

FDA Yes

Narratives and Case Report Forms (CRFs)

15. Is the proposal for submission of narratives and CRFs described in Section 3.3.4 of this document acceptable?

FDA Yes

Electronic Submission

16. Does the Division concur with our proposed electronic submission of documentation as outlined in section 4 of this document? Are there any specific requests/requirements that should be considered to facilitate review of this application?

FDA Only as previously noted.

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 Yes

Regulatory Considerations

Financial Disclosure

We propose to submit the appropriate Financial Disclosure certification in accordance with the Final Rule published in the December 31, 1998 Federal Register for all investigators who enrolled patients in Studies 0102, 0109, 0110 as of February 2, 1999. These studies are the basis for establishing the safety and efficacy of STI571 for the proposed indication. Is this acceptable?

FDA Yes

Pediatric

19. A Proposed Pediatric Study Request (PPSR) was submitted January 20, 2000 to request a Written Request for STI571 in the treatment of pediatric patients with Ph+ leukemias. It is believed that safety information on the pediatric use of STI571 would provide health benefits in the pediatric population. We are awaiting the Division's response to the PPSR.

Priority Review

We believe that STI571 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 Yes but this is a review issue

Joint Review with Canada and/or Japan Health Authorities

We are currently evaluating the feasibility of a global submission of the NDA and would like to explore the possibility of a joint regulatory review of the NDA with Canada and/or Japan. We would like to explore the opportunities with you, including the administrative and regulatory requirements, and obtain FDA's endorsement before moving further forward with discussions with the other involved health authorities.

FDA

This issue will require additional discussion within the agency before a judgment is made. The agency does not currently have plans or procedures for joint reviews. Consequently a joint review does not seem feasible, at present.

3.0 Manufacturing Controls

See CMC review by Dr. Kim.

4.0 Pharmacology

See pharmacology review by Dr. Benson and biopharmaceutics review by Drs. Duan and Gobburu. See also section 1.2 of this review

5.0 Clinical Studies

5.1 Investigators

**APPEARS THIS WAY
ON ORIGINAL**

Table 1 Investigators study 0102

Country	Site #	C.I. Name/Address	# enrolled	# evaluable PPI/PP2	# reportable AEs	# SAEs	# Deaths (<28 days/ after 28 d)	# Premature withdrawals	# Protocol violations	Hematological Response Rates	Cytological Response Rates
UK	0008	Prof. John M. Goldman Imperial College of Medicine, Hammersmith Hosp. Dept Hematology, Du Cane Rd, London W12 0NN	20	16/17	398	52	8/4	13	Diagrp=1	4/20 (20%)	4/20 (20%)
DEU	0010	Oliver G. Ottmann, MD Medizinische Klinik III Univ. Klinik Frankfurt, Theodor-Stern-Kai 7, D-60590 Frankfurt	13	7/8	188	13	1/3	8	Diagrp=3; NEO=2	3/13 (23.1%)	4/13 (30.8%)
DEU	0005	Andreas Hochhaus, MD Klinikum Mannheim der Univ. Heidelberg 3. Medizinische Klinik, Wiesbadener Str 7-11 D-68305, Mannheim	26	21/22	308	37	6/5	18	Diagrp=1	2/26 (7.7%)	3/26 (11.5%)
ITA	0007	Prof. Gianmarco Corneo, Head, Hematology Section, 8° piano B, Nuovo Ospedale San Gerardo via Donizetti 106, I-20052 Monza (MI) & Dr. Carlo Gambacorti-Pascerini, Oncogenic Fusion Proteins Unit, Istituto Nazionale Tumori, Via Venezian 1, I-20133 Milano	7	6/6	72	13	2/0	6	NEO=1	3/7 (42.9%)	0/7 (0%)
ITA	0006	Prof. Sante Tura, Università degli Studi di Bologna, Istituto di Ematologia "L.e A. Seragnoli" Az. Osp. Policlinico "San'Orsola- Malpighi", Via G. Massarenti, 9, I-40138 Bologna	4	2/3	35	5	1/0	2	0	0/4 (0%)	0/4 (0%)
FRA	0002	Prof. Francois Guilhot, C.H.U. de Poitiers, 350 avenue Jacques Coeur, B.P. 577, F-86021, Poitiers	12	8/8	268	30	5/1	6	Diagrp=2; NEO=2	6/12 (50%)	0/12 (0%)
USA	0503	Moshe Talpaz, MD MD Anderson Cancer Center, 1515 Holcombe Boulevard, Box 302, Houston, TX 77030	13	12/12	221	21	2/3	8	Diagrp=1	6/13 (46.2%)	3/13 (23.1%)
USA	0506	Richard T. Silver, MD New York Hospital - Cornell 525 East 68 th Street, Box 581 New York, NY 10021	21	19/19	305	69	11/12	15	Ph=1	4/21 (19%)	5/21 (28.8%)
USA	0501	Brian Drucker, MD Oregon Health Sciences University, Div. of Hematology and Medical Oncology, L592 3181 Southwest Sam Jackson Park Rd, Portland, OR 97201	9	6/7	170	18	1/3	4	Diagrp=1; NEO=1	2/9 (22.2%)	1/9 (11.1%)

Table 2 Investigators study 0109

Country	Site #	C.I. Name/Address	# enrolled	# evaluable PP1/PP2	# AEs	# SAEs	# Deaths (<28 days/ after 28 d)	# Premature withdrawals	# Protocol violations	Hematologic Response Rates	Cytological Response Rates
UK	0008	Prof. John M. Goldman Imperial College of Medicine, Hammersmith Hosp. Dept Hematology, Du Cane Rd, London W12 0NN	21	19/19	441	24	4/2	10	Disgrp=2	12/21 (57.1%)	6/21 (28.6%)
DEU	0010	Oliver G. Ottmann, MD Medizinische Klinik III Univ. Klinik Frankfurt, Theodor-Stern-Kai 7, D-60590 Frankfurt	21	16/11	370	49	1/12	16	Disgrp=2	5/21 (23.8%)	4/21 (19.0%)
DEU	0005	Andreas Hochhaus, MD Klinikum Mannheim der Univ. Heidelberg 3. Medizinische Klinik, Wiesbadener Str 7-11 D-68305, Mannheim	8	5/5	94	6	0/1	3	Disgrp=1	2/8 (25%)	1/8 (12.5%)
ITA	0007	Prof. Gianmarco Corneo, Head, Hematology Section, 8° piano B, Nuovo Ospedale San Gerardo via Donizetti 106, I-20052 Monza (MI) & Dr. Carlo Gambacorti-Passerini, Oncogenic Fusion Proteins Unit, Istituto Nazionale Tumori, Via Venezian 1, I-20133 Milano	14	10/10	310	16	2/1	4	Disgrp=4	12/14 (85.7%)	6/14 (42.9%)
ITA	0006	Prof. Sante Tura, Università degli Studi di Bologna, Istituto di Ematologia "L.e A. Seragnoli" Az. Osp. PoliClinico "San'Orsola-Malpighi", Via G. Massarenti, 9, I-40138 Bologna	8	5/4	88	3	0/1	1	Disgrp=3	7/8 (87.5%)	4/8 (50%)
FRA	0002	Prof. Francois Guilhot, C.H.U. de Poitiers, 350 avenue Jacques Coeur, B.P. 577, F- 86021, Poitiers	11	9/9	345	11	1/0	1	Disgrp=2	8/11 (72.2%)	5/11 (45.5%)
USA	0503	Moshe Talpaz, MD MD Anderson Cancer Center, Houston, TX 77030	58	41/39	1176	81	6/5	23	Disgrp =15; NEO = 1	46/58 (79.3%)	14/58 (24.1%)
USA	0506	Richard T. Silver, MD New York Hospital - Cornell 525 East 68 th Street, Box 581 New York, NY 10021	26	13/16	592	62	5/1	10	Disgrp=6	8/26 (30.8%)	4/26 (15.4%)
USA	0501	Brian Drucker, MD Oregon Health Sciences University, 3181 Southwest Sam Jackson Park Rd, Portland, OR 97201	27	20/20	589	40	7/2	13	Disgrp=4	16/27 (59.3%)	3/27 (11.1%)
USA	0502	Charles Sawyers, MD UCIA Medical Ctr, Factor Bldg K, Rm 11-934, 10833 LeConte Ave, Los Angeles, CA 90095	23	17/20	512	43	4/6	11	Disgrp=3	7/23 (30.4%)	8/23 (34.8%)

Table 3 Investigators study 0110

Country	Site #	C.I. Name/Address	# enrolled	# evaluable PP1/PP2	# reportable AEs	# SAEs	# Deaths (<28 days/ after 28 d)	# Premature withdrawals	# Protocol violations	Hematologic Response Rates	Cytological Response Rates
UK	0008	Prof. John M. Goldman Imperial College of Medicine, Hammersmith Hosp. Dept Hematology, Du Cane Rd, London W12 0NN	14	11/11	272	0	0/0	1	Disgrp=1; NEO = 2	13/14 (92.9%)	6/14 (42.9%)
DEU	0010	Oliver G. Ottmann, MD Univ. Klinik Frankfurt, Theodor-Stern-Kai 7, D-60590 Frankfurt	5	5/5	80	0	0/0	0	0	5/5 (100%)	3/5 (60%)
DEU	0005	Andreas Hochhaus, MD Klinikum Mannheim der Univ. Heidelberg 3. Medizinische Klinik, Wiesbadener Str 7-11 D-68305, Mannheim	30	25/22	279	10	1/0	3	Disgrp=4; Ph- = 1	27/30 (90%)	13/30 (43.3%)
ITA	0007	Prof. Gianmarco Corneo, Head, Hematology Section, 8° piano B, Nuovo Ospedale San Gerardo via Donizetti 106, I-20052 Monza (MI) & Dr. Carlo Gambacorti-Passerini, Oncogenic Fusion Proteins Unit, Istituto Nazionale Tumori, Via Venezian 1, I-20133 Milano	19	18/17	258	3	0/0	0	Disgrp=1	16/19 (84.2%)	11/19 (57.9%)
ITA	0006	Prof. Sante Tura, Università degli Studi di Bologna, Istituto di Ematologia "L.e A. Seragnoli" Az. Osp. PoliClinico "San'Orsola-Malpighi", Via G. Massarenti, 9, I-40138 Bologna	4	4/3	21	0	0/0	0	0	4/4 (100%)	3/4 (75%)
FRA	0002	Prof. Francois Guilhot, C.H.U. de Poitiers, 350 avenue Jacques Coeur, B.P. 577, F- 86021, Poitiers	26	23/23	399	12	0/0	1	Disgrp=2	24/26 (92.3%)	13/26 (50%)
USA	0503	Moehle Talpez, MD MDACC, 1515 Holcombe Boulevard, Box 302, Houston, TX 77030	149	137/129	1445	34	2/1	11	Disgrp =1; NEO = 1	144/149 (96.6%)	76/149 (51.0%)
USA	0506	Richard T. Silver, MD New York Hospital - Cornell 525 East 68 th Street, New York, NY 10021	10	8/7	142	10	0/1	1	Disgrp=2	8/10 (80%)	4/10 (40%)
USA	0501	Brian Drucker, MD Oregon Health Sciences University, 3181 Southwest Sam Jackson Park Rd, Portland, OR 97201	48	42/32	501	5	1/0	3	Disgrp=5; NEO = 1	43/48 (89.6%)	19/48 (39.6%)
USA	0502	Charles Sawyers, MD UCIA Medical Ctr, Factor 10833 LeConte Ave, Los Angeles, CA 90095	53	33/32	1077	14	1/0	4	Disgrp=18 ; NEO = 2	46/53 (86.8%)	28/53 (52.8%)

Table 4 Investigators studies 0102, 0109, 0110

Country	Site #	C.I. Name/Address	Pivotal Study 0109			Pivotal Study 0110			Open Label Study 0102			109+11 enrolled	109+110 +102 enrolled
			# enrolled	Hematol Response	Cytogenetic Response	# enrolled	Hematol Response	Cytogenetic Response	# enrolled	Hematol Response	Cytogenetic Response		
UK	0008	Prof. John M. Goldman Imperial College of Medicine, Hammersmith Hosp. Dept Hematology, Du Cane Rd, London W12 0NN	21	12/21 (57.1%)	6/21 (28.6%)	14	13/14 (92.9%)	6/14 (42.9%)	20	4/20 (20%)	4/20 (20%)	35	55
DEU	0010	Oliver G. Ottmann, MD Medizinische Klinik III Univ. Klinik Frankfurt, Theodor-Stern-Kai 7, D-60590 Frankfurt	21	5/21 (23.8%)	4/21 (19.0%)	5	5/5 (100%)	3/5 (60%)	13	3/13 (23.1%)	4/13 (30.8%)	26	39
DEU	0005	Andreas Hochhaus, MD Klinikum Mannheim der Univ, Heidelberg 3. Medizinische Klinik, Wiesbadener Str 7-11 D-68305, Mannheim	8	2/8 (25%)	1/8 (12.5%)	30	27/30 (90%)	13/30 (43.3%)	26	2/26 (7.7%)	3/26 (11.5%)	38	64
ITA	0007	Prof. Gianmarco Corneo, Head, Hematology Section, 8° piano B, Nuovo Ospedale San Gerardo via Donizetti 106, I-20052 Monza (MI) & Dr. Carlo Gambacorti-Pasolini, Oncogenic Fusion Proteins Unit, Istituto Nazionale Tumori, Via Venezian 1, I-20133 Milano	14	12/14 (85.7%)	6/14 (42.9%)	19	16/19 (84.2%)	11/19 (57.9%)	7	3/7 (42.9%)	0/7 (0%)	33	40
ITA	0006	Prof. Sante Tura, Università degli Studi di Bologna, Istituto di Ematologia "L.e A. Seragnoli" Az. Osp. PoliClinico "San'Orsola-Malpighi", Via G. Massarenti, 9, I-40138 Bologna	8	7/8 (87.5%)	4/8 (50%)	4	4/4 (100%)	3/4 (75%)	4	0/4 (0%)	0/4 (0%)	12	16
FRA	0002	Prof. Francois Guilhot, C.H.U. de Poitiers, 350 avenue Jacques Coeur, B.P. 577, F- 86021, Poitiers	11	8/11 (72.2%)	5/11 (45.5%)	26	24/26 (92.3%)	13/26 (50%)	12	6/12 (50%)	0/12 (0%)	37	49
USA	0503	Moshe Talpaz, MD MD Anderson Cancer Center, Box 302, Houston, TX 77030	58	46/58 (79.3%)	14/58 (24.1%)	149	144/149 (96.6%)	76/149 (51.0%)	13	6/13 (46.2%)	3/13 (23.1%)	207	220
USA	0506	Richard T. Silver, MD New York Hospital - Cornell 525 East 68 th Street, New York, NY 10021	26	8/26 (30.8%)	4/26 (15.4%)	10	8/10 (80%)	4/10 (40%)	21	4/21 (19%)	5/21 (28.8%)	36	57
USA	0501	Brian Drucker, MD Oregon Health Sciences University, Div. of Hematology and Medical Oncology, 3181 Southwest Sam Jackson Park Rd, Portland, OR 97201	27	16/27 (59.3%)	3/27 (11.1%)	48	43/48 (89.6%)	19/48 (39.6%)	9	2/9 (22.2%)	1/9 (11.1%)	75	84
USA	0502	Charles Sawyers, MD UCIA Medical Ctr, Factor Bldg K, Rm 11- 934, 10833 LeConte Ave, Los Angeles, CA 90095	23	7/23 (30.4%)	8/23 (34.8%)	53	46/53 (86.8%)	28/53 (52.8%)	32	8/32 (25%)	2/32 (6.3%)	76	108

5.2 Common Protocol Elements

In order not to repeat information this section details elements that are common to all 3 trials.

5.2.1 Phases of CML and associated efficacy definitions

Chronic phase

1. < 15% blasts in PB and BM
 2. <30% blasts + promyelocytes* in PB or BM
 3. < 20% basophils in PB
 4. 100 x 10⁹/L platelets
 5. No extramedullary involvement other than spleen or liver
- (all 5 criteria must be fulfilled)

Accelerated phase

1. 15% < 30% blasts in PB or BM
 2. 30% blasts + promyelocytes* in PB or BM (but < 30% blasts in PB and BM)
 3. 20% basophils in PB
 4. < 100 x 10⁹/L platelets
- (at least one of the 4 criteria must be fulfilled)

Blast Crisis

1. 30% blasts in PB or BM or
 2. Extramedullary involvement other than spleen or liver
- These two evaluations take preference over chronic and accelerated phase results

5.2.2 Dose interruption and reductions

Grade 2 non-hematologic toxicity

In patients with Grade 2 toxicity persisting despite symptomatic treatment, study drug was to be interrupted until reduction of the toxicity to Grade 1, and then resumed at the same dose. In case of recurrence, study drug was to be interrupted again until reduction of the toxicity to Grade 1 and then resumed at the dose of 300 mg/day for patients at 400 mg/day, at 400 mg/day for patients at 600 mg/day.

In case of grade 3/4 toxicity, study drug was to be interrupted until reduction of the toxicity to Grade 1, and then resumed at 300 mg/day for those patients at 400 mg/day, at 400 mg/day for patients initiated at 600 mg/day.

Hepatic toxicity

In patients with SGOT/SGPT > 3 to 5.0 x ULN at baseline and subsequently experiencing a 3-fold increase in transaminase activity, study drug was to be interrupted until their return to baseline levels before resumption at the same dose. In case of recurrence, study drug was to be interrupted until the return to baseline levels and then resumed at 300 mg/day in patients on 400 mg/day, or at 400 mg/day in patients on 600 mg/day.

Any such patient experiencing a > 3-fold increase in the level of the more elevated of the transaminase variables was to have study drug interrupted until their return to the baseline level, followed by resumption of study drug at a reduced dosage as described above.

Grade 3/4 hematologic toxicity

No dose modifications were to be performed during the first 28 days of therapy.

No dose interruptions or reductions were performed for Grade 1 and 2 hematologic toxicity.

After at least 28 days of therapy, and in patients with grade 4 neutropenia ($ANC < 0.5 \times 10^9/L$) persisting for ≥ 2 weeks, a bone marrow aspirate and biopsy were to be performed to assess bone marrow (BM) cellularity and percentage blasts. According to the values obtained the following dosage modification procedures were to be followed:

For BM hypocellularity (< 10%), blasts < 10%):

In patients at 400mg/day

- dose-reduction to 300mg/d
- if persistence of grade 4 neutropenia for two weeks, the bone marrow aspirate and biopsy were to be repeated. In case of hypocellular BM and blasts <10%, the dose was to be reduced to 200 mg/day.
- if persistence of grade 4 neutropenia for a further two weeks, with a repeat BM evaluation showing hypocellularity and blasts <10%, study drug was to be interrupted until $ANC \geq 1.0 \times 10^9/L$ before resumption at 400 mg/day.

In patients at 600 mg/day dose reduction to 400 mg/day if persistence of grade 4 neutropenia for two weeks, the bone marrow aspirate and biopsy were to be repeated. In case of hypocellularity and blasts <10%, the dose was reduced to 400 mg/day if persistence of grade 4 neutropenia for a further two weeks with a repeat BM evaluation showing hypocellularity and blasts <10%, study drug was to be interrupted until $ANC \geq 1.0 \times 10^9/L$ before resumption at 600 mg/day.

In patients at 800 mg/d (after escalation from 600mg/d)
0 as above but with the initial dose-reduction being to 600 mg/d

BM cellularity >10% and/or blasts >10%,

treatment was to be continued at the same dose (400 or 600 mg/day). if persistence of grade 4 neutropenia for ≥ 2 weeks, the above procedure was to be followed.

In case of recurrence of blast crisis, confirmed by a BM biopsy, full dose (400 or 600 mg/day) could be resumed.

Dosing,

STI571 was originally supplied by Novartis as 25, 50 and 100 mg capsules. With the implementation of Amendment 2 and the increase in dose from 400 mg to 600 mg for blast crisis and accelerated disease patients, STI571 was then supplied as 100 mg capsules packaged bottles. Medication labels complied with the legal requirements of each country and were printed in the local language.

Patients received continuous once daily oral administration of STI571 at a dose of 400 mg (chronic phase) or 600 mg for 24 weeks. For patients who initiated trial treatment at a dose of 400 mg/day, intra-patient dose escalation from 400 mg to 600 mg daily could be approved on a patient-by-patient basis after discussion between the investigator and the sponsor (Amendment 1).

Patients who were resistant or relapsed while receiving treatment with STI571 at a dose of 600 mg/day could have the dose increased to 800 mg administered as 400 mg twice daily. The decision to dose-escalate was made by the investigator and the sponsor on a case by case basis (Amendment 2).

After completing 24 weeks of therapy, patients were eligible to receive additional therapy if, in the opinion of the investigator, the patient was benefiting from treatment with STI571, and there were no safety concerns.

STI571 was to be taken in the morning, two hours after breakfast, by patients on a once daily regimen; and in the morning and evening (two hours after breakfast and dinner) by patients on a twice-daily regimen (800mg/d). Because STI571 is a local irritant, it was to be taken in the sitting position accompanied by a large glass of water (250 ml). Following demonstration of the absence of a significant food interaction patients were requested to take study drug with meals (amendment 3).

5.2.3 Concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient were allowed, provided their use was documented in the patient records and on the Concomitant Medication/Non-Drug Therapy CRF.

- **Growth factors** were permitted at the discretion of the investigator for patients with neutropenic (ANC < 0.5 x 10⁹/L) fever.
- **Anticancer agents** including chemotherapy and other biological agents were not permitted with the exception of the following during the first 28 days when required to control elevated blast/platelet counts:

-Anagrelide (Agraylin®) or leukapheresis (2 procedures/week and (54 procedures overall)
-hydroxyurea (5g/d) for a maximum of seven days

The use of drugs that significantly alter gastric pH (e.g., H-2 blockers and proton pump inhibitors) was to be avoided (possible interference with the absorption of STI571). When needed, antacids could be administered at least four hours following study drug administration. For patients in whom pharmacokinetic profiles were performed, antacids were to be avoided completely on the days prior to and during blood sampling. This restriction was removed when additional pharmacokinetic data became available showing an absence of such an interaction.

All patients were to receive allopurinol 300 mg administered as a single oral daily dose beginning ideally 48-hours prior to study drug administration. As the white blood cell count stabilized, allopurinol could be discontinued at the discretion of the investigator.

5.2.4 Visit Schedule

The visit schedule and assessments to be performed at each visit are described in Table 5 (first 24 weeks and Table 6 (beyond 24 weeks).

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ON ORIGINAL**

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ON ORIGINAL**

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ON ORIGINAL**

Table 5 Visit schedule and assessments - Part 1 (24 weeks)

Week	Month 1												2				3				4		5		6		End of part 1			
	-7to0	1	3	5	8	10	12	15	17	19	22	24	26	29	36	43	50	57	64	71	78	85	99	113	127	141	155	169		
Study Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28		
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28		
Demographics/ Medical conditions/ Disease history/ Prior antineoplastics	x																													
ECG evaluation	X				X																									
Cancer symptoms	X																						X					X		
Physical examination/ Vital signs	X													X				X					X		X		X	X		
Perf Status	X																	X					X					X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Biochemistry	X	X			X			X			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Extramedullary involvement	X													X				X					X					X		
Bone marrow analysis (a)	X													X				X				X		X		X		X		
Response assessment														X				X				X						X		
Blood sample collection (b)		X	X		X	X																						X		
Dosage admin. record		X	Completed as needed																											
Adverse events		Completed as needed																												
Concom. medications/	x	Completed as needed																												
Study/study phase completion (c)		Completed as needed																												
Survival (d)		Completed as needed																												

- a) Cytogenetic studies required at baseline, Week 13 and 25, or when patient discontinued. If Grade 4 neutropenia (ANC < 0.5 x 10⁹/L) presented Day 14 or later, aspirate and biopsy were required.
- b) PK sampling: US centers ONLY - Day 1 Blood sample collection: immediately prior to study drug administration and following drug administration at 0.5, 1, 1.5, 2, 4, 8, 24 (no drug), 48 (no drug) and 72 (pre dose) hours. Day 8 blood sample collection: immediately prior to study drug administration and at the following timepoints following drug administration: 0.5, 1, 1.5, 2, 4, 8, 24, 48 and 72 hours. The patient was not to take any medication on the morning of Days 9 and 10 and was to resume taking trial medication on the morning of Day 11 AFTER the final (72-hour) blood sample had been taken. All patients accrued in US centers were to have a blood sample drawn exactly 24 hours after the last dose of STI571.
- c) Completed at end of Week 24, or at any time patient discontinued study drug.
- d) Follow-up for survival was required on all patients following discontinuation of study drug (monthly for the first 3 months, thereafter every 3 months until death or patient lost to follow-up).

Table 6 Visit schedule and assessments - Part 2

Month	7	8	9	10	11	12	14	16	18	20	End of study
Week	29	33	37	41	45	49	-	-	-	-	-
Visit	29	30	31	32	33	34	35	36	37	38	-
Physical examination/ Vital signs	X	X	X	X	X	X	X	X	X	X	X
Performance status	X	X	X	X	X	X	X	X	X	X	X
Hematology/ Biochemistry	X	X	X	X	X	X	X	X	X	X	X
Extramedullary involvement			X			X			X		X
Bone marrow analysis (a)			X			X			X		X
Response status			X			X			X		X
Dosage admin. record	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	Completed as needed									X
Concom. medications/	X	Completed as needed									X
Study completion (Part 2)											X
Survival status (b)											X

- a) Bone marrow including cytogenetics to be assessed every three months for the first six months and every four months thereafter.
- b) Follow-up for survival was required on all patients following discontinuation of study drug (monthly for the first 3 months, thereafter every 3 months until death or patient lost to follow-up).

5.2.5 Efficacy assessments

Hematologic response was the primary efficacy parameter in studies 0102 and 0109 (Blast crisis and accelerated phase disease, respectively) and a secondary efficacy parameter in study 0110. Major cytogenetic response was the primary efficacy parameter in study 0110.

Hematologic response (0102 and 0109) was divided into 3 sub-categories Complete hematologic remission (CHR), No evidence of leukemia (NEL), Return to chronic phase (RTC), which are defined below. Otherwise, patients were classified as:

"No response" when

Any value indicated the absence of response (even if values were not available for all variables)

Additionally, the following two categories were used in the Novartis calculation of hematologic response:

"Not assessable" when

The available values did not allow the determination of any of the categories above or the investigator did not assess the response.

"Not done" when

The investigator did not perform the tests for hematologic response at a given visit.

Complete hematologic response-

The complete hematologic response assessment was based on hematology values, bone marrow evaluation and extramedullary disease evaluations. If laboratory values were not assessed at the respective visit but were done within 14 days before the efficacy assessment of extramedullary disease, the values were carried forward from the previous lab sample and used for analysis. As promyelocytes in peripheral blood were not recorded separately in the CRF, but rather the sum of early forms (which also included metamyelocytes and myelocytes), this value was used to calculate hematologic response. If early forms were <5%, the criteria for CHR (metamyelocytes + myelocytes <5% and promyelocytes =0%) were considered to be fulfilled. As extramedullary disease was evaluated only every 3 months, the last available assessment was carried forward until a new assessment was made. This was done unless the prior evaluation showed no involvement whereas the next evaluation did: in this case the results were not carried forward as the appearance of extramedullary disease may have occurred in between the assessments. Complete hematologic response (CHR) was assigned only if the response was confirmed ≥ 4 weeks later, without any intermediary value indicating "no response" or "progression". As assessments were not always made strictly according to schedule, this time stipulation was taken as ≥ 26 days. For patients who discontinued treatment, assessments were taken into consideration up until 14 days after the last dose of STI571. If patients had only one post-baseline assessment, they were assigned as "Not assessable" unless they discontinued due to unsatisfactory therapeutic effect, or progressed to blast crisis or accelerated phase (in which case they were classified as "progression") or died while on treatment with STI571 (classified as "death").