CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-335/S-004

Medical Review(s)

New Drug Application
Gleevec™ (imatinib mesylate)

Supplemental NDA 21-335:
(S-004)

FDA Center for Drug Evaluation and Research
Division of Oncology Drug Products

Clinical supplemental NDA Review

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Clinical Review of NDA 21-335

Executive Summary[ExecSumm2]

I Recommendations

1 Recommendation on Approvability

In the study under review, Gleevec has demonstrated efficacy in the on the surrogate endpoints of increased hematologic response and cytogenetic response rates compared with interferon. Gleevec has also demonstrated efficacy in the clinical benefit of prolonging time to progression and time to accelerated phase and blast crisis, however the durability of that effect has not yet been demonstrated. No effect has been demonstrated on the clinical benefit of prolonging survival. The safety and tolerability of Gleevec has been demonstrated in 1663 patients with CML studied in 5 registration trials. The most frequently reported drug-related adverse events were nausea, vomiting, diarrhea, edema, and muscle cramps.

I therefore recommend Accelerated Approval, under CFR§314.510 Subpart H, for Gleevec (Imatinib) in the treatment of newly diagnosed Philadelphia chromosome-positive CML patients.

2 Recommendation on Phase 4 Studies and/or Risk Management Steps

Phase 4 commitment required for Accelerated Approval (subpart H):

To provide interval follow-up safety and efficacy information on study 106 annually, for three additional years, and survival data and serious adverse event data thereafter for another three years.

Other phase 4 studies:

To conduct a prospective study performed in patients receiving both Gleevec and a potent CYP3A4 inducer such as phenytoin, phenobarbital, or carbamazepine and submit a final study report. The purpose of this study is to determine the dose of Gleevec that is necessary to

produce similar AUCs in these patients on enzyme inducers to those achieved in adult patients receiving the usual recommended dose (400 mg/day).

II Summary of Clinical Findings

1 Brief Overview of Clinical Program

Gleevec (Imatinib, GLEEVEC) is an orally bioavailable tyrosine kinase inhibitor. Gleevec specifically inhibits the activity of abl kinase, a protein that is the product of a fusion gene found on the 9:22 chromosome translocation known as the Philadelphia Chromosome. This genetic abnormality is the molecular hallmark of chronic myelogenous leukemia (CML). Gleevec has been shown in previous single arm registration studies to cause hematologic responses in patients with CML in advanced stages, and in May of 2001, was granted accelerated marketing approval under the subpart H regulations for the treatment of advanced stages of CML. The current trial under review enrolled 1106 patients with newly diagnosed Philadelphia chromosome-positive CML. Five hundred fifty three patients were randomized to the Gleevec treatment arm and 553 patients were randomized to receive interferon. A total of 1663 patients with various stages of CML have been exposed to Gleevec in five registration trials.

2 Efficacy

The primary efficacy endpoint was time to progression. The definition of progression included death during treatment, the development of accelerated phase or blast crisis, loss of complete hematologic or cytogenetic responses, and increasing white blood counts that were reviewed by the study monitoring committee and certified as therapeutic failures appropriate for crossover. The planned cutoff date for the TTP analysis was the date of the 385th event, however the progression analysis was performed early because of the highly significant results of the interim analysis of cytogenetic responses at one year. FDA and the sponsor agreed that the interim analysis of TTP results at 127 progression events are quite highly statistically significant, favoring the Gleevec treatment arm. The Gleevec vs. IFN+Cytarabine hazard ratio was 0.183 (95% C.I. of 0.117, 0.285) and the difference was highly statistically significant by log-rank test. Analysis of the Kaplan-Meier plot (Figure 11 and Table 33) confirms that the Gleevec treatment arm has a statistically significantly longer time to progression than the interferon treatment arm. The sponsor and FDA agree that a significantly higher percentage of patients progressed to accelerated phase on the interferon treatment arm compared with the Gleevec treatment arm, and that was true in both the first line as well as the intent to treat (ITT) analyses, despite the high percentage of crossovers to the Gleevec arm. Statistical modeling suggests that it is highly probable that the results will still be statistically significant favoring the Gleevec treatment arm at the planned analysis after 385 events.

Secondary efficacy endpoints included complete hematologic response rate and duration, major cytogenetic response rate and duration, survival, and patient-reported "quality of life." The results of the FDA and sponsor's analysis of complete hematologic and cytogenetic response rates are summarized in the following Table:

Table 1: FDA and Sponsor's Confirmed Response Rates

Analysis	Gleevec N=553	IFN+Ara-C N=553
Sponsor's CHR rate n (%)	523 (94.6%)	423 (76.5%)
95% CI	[92 3%, 96.3%]	[72.7%, 80.0%]
Fisher's Exact Test	p<0.001	
FDA CHR rate n (%)	534 (96.6%)	451 (81.5%)
Fisher's Exact Test	p<0.001	
Sponsor's Confirmed Cytogenetic Response Rates		
Number of MCyR (%)	419 (75.8%)	67 (12.1%)
95% C.I.	0.720-0.793	0.095-0.151
Fisher's Exact Test	< 0.001	
Number of CCyR	297 (53.7%)	15 (2.7%)
FDA Confirmed Cytogenetic Response Rates		
Number (%) confirmed MCyR	326 (59.0%)	41 (7.4%)
95% C.I.	54.7%, 63.1%	5.4%, 9.9%
Fisher's Exact Test	$1\ 24\times10^{-80}$	
Number (%) confirmed CCyR	146 (26.4%)	18 (3.3%)
95% C.I.	22.8%, 30.3%	1.9%, 5.1%
Fisher's Exact Test	7.33×10^{-30}	

The sponsor and FDA agree that a statistically significantly higher proportion of chronic phase CML patients achieved a complete hematologic response (CHR) with Gleevec compared with interferon and cytarabine. Onset of CHR appeared to be more rapid and the responses appeared to be at least as durable on Gleevec compared with interferon and cytarabine over the study duration. Although median duration of complete hematologic response was not reached, 11 patients (2.1%) on Gleevec had lost their complete hematologic responses while 46 patients on interferon had lost their complete hematologic responses at data cutoff. All analyses of response rates favored the Gleevec treatment arm and were highly statistically significant.

Several issues affected the interpretation of efficacy results. The two treatment arms appeared to be fairly well balanced with respect to most known adverse prognostic characteristics. There were more major protocol deviations on the interferon treatment arm compared with Gleevec. More patients on the interferon arm dropped out without receiving interferon. The overall dose intensity of interferon achieved in study 106 was 56% of the target dose, compared with a 97% of planned dose intensity for patients on the Gleevec arm. Dose intensity on the active control arm was somewhat less than in previous published studies of interferon in CML, however the FDA reviewer concluded that the efficacy results were sufficiently compelling to offset the possible effects of the decreased dose intensity on the active control arm.

The most significant factor affecting efficacy results was the amount of crossover that occurred in this trial. The sponsor asserted that crossovers were necessary for ethical reasons and to encourage accrual to the trial. All crossovers had to be approved by a study monitoring committee. Almost 40% of the patients who began on the Interferon/Cytarabine arm crossed over to the Gleevec arm, whereas only 1% of patients originally on the Gleevec arm crossed over to the Interferon/Cytarabine arm. The extensive crossover could cause an overestimation of the response rates in the active control arm, thereby obscuring the difference between arms in the intent to treat (ITT) analysis. Hematologic responses of patients who crossed over from interferon to Gleevec would increase the responses rates attributed to the interferon arm. The CHR rates on the interferon arm were 54% and 76% in the sponsor's analysis of first line and the ITT populations, respectively; whereas Gleevec CHR rates were essentially unchanged at 94% between the two populations. Major Cytogenetic responses were similarly affected. The differences in ITT progression events would also tend to be obscured by extensive crossover, assuming that crossing over from interferon to Gleevec would significantly decrease the risk of progression. The extensive crossover will also make survival results difficult to interpret.

3 Safety

Gleevec has been compared to a present standard treatment consisting of the combination of Alpha interferon + Ara-C in a RCT of first line treatment of 1106 patients with newly diagnosed CML in chronic phase. Median follow-up of 551 Gleevec dosed patients is 421 days.

Gleevec has substantially less severe adverse effects than the present standard treatment (Alpha Interferon with or without Ara-C). The most common adverse effect is edema seen in 54% of patients. But only 0.6% of patients have grade 3 or 4 edema. The other most common adverse effects on a per patient basis are nausea (43%), muscle cramps (33%), fatigue (31%), diarrhea (30%), headache (29%), arthralgia (27%), and myalgia (21%). The only ≥ grade 3 Gleevec adverse events seen in > 1% of patients are neutropenia (14%), thrombocytopenia (7%), anemia (3%), elevated SGOT (3%), elevated SGPT (4%) and arthralgia (2%).

The median duration of survival in these patients may be 6 years or more. Gleevec safety evaluation is adequate for marketing approval for this indication, however the Applicant should be required to submit annual updates on this trial.

4 Dosing

The protocol-specified starting dose of Gleevec was 400 mg per day, and 86% of all doses given were at the 400 mg dose level. The approved dose is 400 mg for chronic phase after interferon failure and 600 mg for accelerated phase. Gleevec appears to be well tolerated at doses up to

800 mg, and there appears to be a wide therapeutic window. Eleven percent of all doses were reduced, and 2% of all doses were increased above the recommended starting dose up to a maximum dose of 800 mg per day in the trial under review. The recommended dosage of Gleevec in the current label is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis. Gleevec is given orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

5 Special Populations

5.1. Effects of Gender

The FDA and Applicant did not find any gender effects on efficacy. Specifically, no gender effect is apparent on the primary efficacy endpoint of Time to Progression or on Time to Accelerated Phase or Blast Crisis. There were several observed gender effects on safety. Using a Fisher's Exact Test $P< 0.005$ as criterion and ignoring adverse effects that can occur only in one gender, the following adverse effects appear to be more frequent in women: periorbital edema, edema NOS, peripheral edema, face edema, rigors, nausea neutropenia and headache. There were no adverse effects that appeared to be more frequent in men. These differences were not attributable to differences in weight between men and women.

5.2. Effects of Age

Efficacy was compared between patients < 60 and patients ≥ 60 years of age. There is no apparent age effect on the primary efficacy endpoint of Time to Progression or on Time to Accelerated Phase or Blast Crisis. There is a suggestion within the Gleevec treatment group that Gleevec may be more effective in patients < 60 years of age than in patients ≥ 60 years of age, but this is not conclusive. There is no apparent age difference in efficacy within the Interferon + Ara-C treatment group. The FDA found that the following adverse events were more commonly reported in patients ≥ 60 years: Hematoma, hemorrhoids, fungal infections, falls, gout, eye discharge, dry eye, face edema, and eyelid edema.

5.3. Effects of Race

There were insufficient numbers of patients in the non-Caucasian races to permit analyses.

Clinical Review

I. Introduction and Background

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder characterized by progressive granulocytosis, marrow hypercellularity, and splenomegaly. CML occurs with an incidence of about 1.3 per 100,000 and accounts for about 15 percent of newly diagnosed cases of leukemia in adults. The median age at diagnosis is 50-60 years and CML is slightly more common in men. The course of the disease is characteristically tri-phasic: a chronic phase lasting three to six years is followed by transformation to accelerated and then blast phases of short duration. The chronic phase is relatively stable and responds to therapy, but it eventually evolves into an intermediate, accelerated phase, in which increasing doses of hydroxyurea are needed to control disease, followed by a blast phase. Blast-phase disease resembles acute leukemia. Its phenotype is myeloblastic in 70 to 80 percent of patients and lymphoblastic in 20 to 30 percent. The median survival of patients in accelerated phase is 1 to 1.5 years, and in blastic phase, 3 to 6 months.[1]

The molecular biology of CML has been well described. The hallmark of CML is the Philadelphia chromosome, found in 90 to 95% of patients.[2] This cytogenetic abnormality consists of an abnormally short chromosome 22 resulting from a reciprocal translocation of chromosomes 9 and 22. These consist of the breakpoint cluster region (*BCR)* and *ABL* genes, which combine to form a *BCR-ABL* fusion oncogene. The product of the *BCR-ABL* gene, the BCR-ABL protein, is a constitutively active protein tyrosine kinase with an important role in the regulation of cell growth. The *ABL* gene encodes a tyrosine kinase whose activity is tightly regulated. Both genes are truncated in the formation of the t (9:22) reciprocal translocation that characterizes CML cells, and two fusion genes are generated: *BCR-ABL* on the derivative 22q– chromosome (the Ph chromosome) and *ABL-BCR* on chromosome 9q+. Insertion of the *BCR-ABL* gene into murine stem cells induces a leukemia-like disease in mice.[3]

Cytogenetic analysis is the gold standard diagnostic test in chronic myelogenous leukemia. However, in 10% of patients with chronic myelogenous leukemia, Philadelphia positivity cannot be demonstrated by cytogenetic studies. Molecular analysis can detect *BCR-ABL* rearrangements in up to one half of these patients. Genomic PCR and Southern blot assay can determine the exact breakpoints of the fusion genes. Reverse transcriptase (RT) PCR and Northern blot analysis detect *BCR-ABL* transcripts at the RNA level. Western blot analysis or immunoprecipitation demonstrate the $p210^{bcr\text{-}abl}$ protein by using monoclonal antibodies against Bcr and Abl.[4]

Therapy of CML initially involved the use of busulfan to control the myeloproliferation. Patients with chronic-phase CML more recently have been treated with hydroxyurea and interferon alfa. Hydroxyurea is administered orally, typically returns blood counts to normal, shrinks the spleen, and is easier to monitor than busulfan. Interferon must be administered subcutaneously, has noticeable side effects, and controls blood counts in only about two thirds of patients. Nevertheless interferon has been shown to induce remissions, reduce or eliminate the expression of the Philadelphia chromosome, and prolong survival.[5] About 25 percent of CML

patients have a major cytogenetic response (defined as the disappearance of the Ph chromosome from at least 66 percent of marrow cells in metaphase) and about 10 percent have a complete cytogenetic response (defined as the reversion to Ph-chromosome–negative status). Cytarabine in combination with alpha interferon was reported to provide additional benefits in terms of cytogenetic response, hematologic response, and 3 year survival rates compared with alpha interferon alone in a French study of 721 patients with previously untreated CML.[6] An Italian study of 538 Philadelphia-chromosome positive minimally pretreated CML patients, confirmed the benefit of the addition of cytarabine for cytogenetic response but not for hematologic response or for survival.[7]

Table 2: Studies of Interferon vs IFN + Ara C in CML

Study	N	Treatment	CHR %	MCyR	Survival
Guilhot[6]	311	IFN +Ara-C	66*	41*	*
	314	IFN	55*	24*	
Baccarini[7]	275	IFN+ Ara-C	62	28*	NS
	263	IFN	55	18*	

* Statistically significant NS = not significant

Despite improvements in therapy, CML remains incurable by conventional therapy. Residual disease remained detectable even in patients who attain a remission, and the majority of patients relapsed and eventually succumb to the disease. Myeloablation followed by allogeneic stem cell transplantation has been shown to be curative in CML, however the transplant-related mortality has been reported as high as 50% in patients over 30 years of age and in unrelated donors [8] Two-year disease-free survival ranges from 60% in younger patients transplanted in chronic phase to 30% or less for unrelated donors.[9]

The efficacy of treatments for CML in clinical trials has commonly been measured in terms of survival and hematologic and cytogenetic response rates. Time to progression has been less commonly used as a measure of treatment effect. Meyskens, et. al. reported on a SWOG study which found that the addition of of vitamin A had no significant effect on survival or time to progression of 153 patients with CML treated with busulfan. Progression was defined as (1) an increasing leukocyte count with or without progressive anemia; plus (2) more than 25% blasts plus promyelocytes in the bone marrow and/or peripheral blood; plus (3) progressive splenic enlargement in a non- splenectomicized patient. [10] The Italian Cooperative Study Group compared interferon with conventional treatment with busulfan and hydroxyurea in 322 patients with previously untreated or minimally treated Philadelphia chromosome-positive chronic myeloid leukemia. This trial found increased cytogenetic responses, survival, and time to accelerated phase in the group treated with interferon alfa-2a (218 patients) compared with conventional chemotherapy (104 patients). [11] Progression to accelerated phase was defined by at least two of the following five predetermined criteria: a peripheral-blood sample containing more than 10 percent blast cells or more than 30 percent blast cells and promyelocytes; a bone marrow aspirate containing more than 15 percent blast cells or more than 50 percent blast cells and promyelocytes; a spleen that could be palpated more than 10 cm below the left costal margin and a white-cell count of less than 25,000 per cubic millimeter; involvement of the central nervous

system, bone, lymph nodes, or other extrahematologic sites; and karyotypic evaluation revealing trisomy Ph[1], trisomy 8, or iso chromosome 17. QOL measurements have been used in the evaluation of effects of therapy in patients with CML.[12]

Imatinib (Gleevec, Novartis, Basel, Switzerland), formerly referred to as GLEEVEC and CGP 57148B, is an inhibitor of specific protein tyrosine kinases that were targeted to the platelet-derived growth factor (PDGF) receptor.[13] It was developed in a search for a selective kinase inhibitor of the constitutively active fusion product abl kinase.[14] Imatinib was shown to block proliferation and induces apoptosis of Bcr-Abl-expressing CML and acute lymphocytic leukemia cell lines.[15] In clinical studies, imatinib was relatively well tolerated, side effects were usually mild to moderate in severity and most frequently included nausea, vomiting, diarrhea, edema, muscle cramps, hemorrhage, musculoskeletal pain, skin rash and peripheral edema.

Imatinib was approved by the Food and Drug Administration in May 2001 for the treatment of CML in accelerated phase and blast crisis and in chronic phase after interferon therapy, and in February 2002 for the treatment of gastrointestinal stromal tumors. Approval was based on response rates from single arm studies in three groups of patients: Chronic phase after interferon, accelerated phase, and blast crisis.[16] The response rates are listed below in Table 1:

Table 3 Hematologic Responses in CML Patients in Phase 2 Clinical Studies

	Chronic Phase, Following IFN (n=532)	**Accelerated Phase (n=235)**	**Myeloid Blast-Crisis (n=260)**
	400 mg	600 mg n=158 400 mg n=77	600 mg n=223 400 mg n=37
	% of patients [CI 95%]		
Hematologic Response[a]	93% [91.0-95.4]	69% [63.0-75.2]	31% [25.2-36.8]
Complete hematologic response (CHR)[b]	93%	37%	7%
Return to chronic phase (RTC)	Not applicable	20%	19%
Major Cytogenetic Response[c]	53% [48.7-57.3]	19% [14.3-24.8]	7% [4.2-10.7]

[a] Hematologic response criteria (all responses to be confirmed after =4 weeks):
CHR: Chronic phase study [WBC <10 x10^9/L, platelet <450 x10^9/L, myelocytes+metamyelocytes <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement] and in the Accelerated and blast crisis studies [ANC =1.5 x10^9/L, platelets =100 x10^9/L, no blood blasts, BM blasts <5% and no extramedullary disease] 20 x10^9/L (accelerated and blast crisis studies): RTC: <15% blasts BM and PB, <30% blasts+promyelocytes in BM and PB, <20% basophils in PB, no extramedullary disease other than spleen and liver (accelerated and blast crisis studies) BM=bone marrow, PB=peripheral blood
[c] Major cytogenetic Response: A major response combines both complete and partial responses: complete (0% Ph+ metaphases), partial (1%-35% Ph+ metaphases)

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

Established Name: imatinib mesylate

Proprietary Name: Gleevec™

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

Drug Class: Antineoplastic (Tyrosine kinase inhibitor)

Current Indications:

Gleevec (imatinib mesylate) is indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). (See CLINICAL STUDIES: Gastrointestinal Stromal Tumors.)

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

Proposed indications:

Gleevec™ (imatinib mesylate) is indicated for the treatment of patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (CML). It is also indicated for the treatment of patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). (See CLINICAL STUDIES: Gastrointestinal Stromal Tumors.) The effectiveness of Gleevec in GIST is based on objective response rate (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

2 State of Armamentarium for Indication(s)

The following products are indicated for the treatment of chronic myelogenous leukemia in the United States:

MUSTARGEN®, (Merck) (Mechlorethamine HCl for Injection) MUSTARGEN, administered intravenously, is indicated for the palliative treatment of Hodgkin's disease (Stages III and IV), lymphosarcoma, chronic myelocytic or chronic lymphocytic leukemia, polycythemia vera, mycosis fungoides, and bronchogenic carcinoma.

MYLERAN® (GlaxoSmithKline) MYLERAN (busulfan) is indicated for the palliative treatment of chronic myelogenous (myeloid, myelocytic, granulocytic) leukemia

MYLOCEL™ (MGI) hydroxyurea. Significant tumor response to MYLOCEL™ (hydroxyurea tablets) has been demonstrated in melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic, or inoperable carcinoma of the ovary.

ROFERON®-A (Roche Laboratories) (Interferon alfa-2a, recombinant) Roferon-A is indicated for the treatment of ... chronic phase, Philadelphia chromosome (Ph) positive chronic myelogenous leukemia (CML) patients who are minimally pretreated (within 1 year of diagnosis).

GLEEVEC™ (Novartis) (imatinib mesylate) Gleevec™ (imatinib mesylate) is indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy

3 Important Milestones in Product Development

May 1996	Drucker, et. *al.* publish report on a 2-phenylaminopyrimidine BCR ABL tyrosine kinase inhibitor with ability to suppress the growth of BCR-ABL positive cells[17]
April 1998	IND [redacted] submitted: A phase I, dose-finding study to determine the safety, tolerability, pharmacokinetic and pharmacodynamic profiles, and to evaluate for preliminary anti-leukemic effects of CBP 57148B in patients with chronic myeloid leukemia who are resistant to interferon-alpha.
Dec 7, 1999	End of phase 1 meeting: Novartis proposed a randomized controlled trial in patients receiving initial treatment for CML. The arms would probably be STI alone versus STI + Interferon versus Cytarabine + Interferon.

May 3, 2000: Meeting regarding registration in the first line treatment of newly diagnosed chronic phase CML, study 106:

- 6-month complete hematologic response rate was not acceptable as a primary endpoint, since it has not been demonstrated to be an adequate surrogate for survival or other clinical benefit.

- Improved QOL as measured by the proposed FACT-BRM would not serve as the basis for accelerated approval. Demonstration of a strongly favorable effect on other QOL measures such as disease related symptoms would be required.

- Demonstration of superiority with major cytogenetic response (MCR), as a primary endpoint, at 24 months may be acceptable for accelerated approval.

- The primary analysis will be intention-to-treat, i.e., patients with a MCR who were randomized to interferon and crossed over to GLEEVEC before 24 months will be counted as a responses on the interferon arm. Extensive crossover will reduce the ability of the trial to detect differences in MCR. Crossover too early for too many patients would impair the capacity to assess the effect of treatment on overall survival and time to blast crisis or accelerated phase.

- The FDA suggested [redacted]

  The sponsor never agreed to this.

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

- The choice of Interferon + Hydroxyurea was acceptable as the comparator regimen on the basis of the report of the French CML Study Group NEJM 337:223-9 (1997).

Statistical Issues:

- The log-rank test should be the primary analysis for time to event endpoints.

- Cox regression analyses should be considered as secondary analyses.

August 31, 2000: End of Phase 2 meeting to discuss the development plan in newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase. Novartis agreed to the following:

Superiority of Time to Progression (TTP) was agreed as the primary endpoint. Using TTP as the primary endpoint there will be fewer crossovers overall and much fewer early crossovers.

The FDA suggested that the definition of progression should 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

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

Time to Treatment Failure (TTF) is not acceptable to the FDA 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, capacity to respond may be a good prognostic feature.[6]
- McyR is not a compelling endpoint. There is 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.

May 10, 2001 Gleevec™ (imatinib mesylate) was granted marketing approval in the United States (NDA 21-335) for treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Approval was based on response rates in single arm trials.

March 26, 2002: Pre sNDA written agreements reached with respect to sNDA submission of Gleevec for first-line CML.

- FDA agreed to the sponsor's proposed definition of patients populations, treatment variables (first line treatment, second line treatment, crossovers), efficacy variables and endpoints, safety analyses, and statistical analysis methods.
- Presentation of data by treatment period (ITT approach, first line treatment, second line treatment) and the structure of safety tables and listings were also acceptable.
- Efficacy analyses: definition of endpoints (CHR, MCR at 12 months, time to progression, time to accelerated phase or blast crisis, overall survival), definitions and timing of events/censored observations
- FDA reminded the sponsor that failure to achieve a CHR at 6 months or MCyR at 12 months were not considered to be acceptable efficacy endpoints.
- The FDA agreed to the sponsor's proposed structure of the ISS, with a side-by-side presentation of the safety data from the phase III study 0106, the pediatric study 0103, SAE from the phase II trials and an update of the GIST phase II study 2222.

- Regarding cytogenetic responses: unconfirmed responses should not be counted. If an individual has a CCyR on one occasion and a PCyR on a second evaluation it will be scored as a PCyR. If the order is reversed and no subsequent study is done it is still a PCyR.
- The FDA expressed concerns regarding the maturity of the data and robustness of the data on PFS based on the results of study 0106 after a minimum of 12 months of follow-up.

June 28, 2002: sNDA 21-335 for newly diagnosed CML is filed

August 14, 2002 Sponsor presented sNDA data from study 106 to Division. 45 day filing meeting

4 Important Issues with Pharmacologically Related Agents

Receptor tyrosine kinases (RTKs), such as the PDGF-R, bcr-abl, epidermal growth factor receptor, and insulin-like growth factor receptors, are expressed in a variety of tumors. The RTC is activated when the appropriate growth factor (ligand) binds extracellular portions of the receptor. Stimulation of these signal transduction pathways tends to cause cell proliferation, and inhibition tends to cause inhibition of proliferation. This finding has led to the development of a variety of tyrosine kinase inhibitors for the treatment of malignancy.

Gleevec was the first specific biochemical tyrosine kinase inhibitor to achieve marketing approval in the U.S., however there are numerous receptor kinase signaling protein inhibitors in clinical oncology trials with a variety of specific molecular targets and disease activities. Herceptin is a monoclonal antibody targeting the HER2 neu tyrosine kinase receptor with activity and marketing approval in breast cancer. Iressa is an epidermal growth factor tyrosine kinase inhibitor with activity in lung cancer. SU101 is an isoxazole derivative that inhibits the platelet-derived growth factor receptor (PDGF-R)/Flk-1 family of receptor tyrosine kinases. These products have variable specificity for a particular receptor, and, in the case of Gleevec, the presence of a similar receptor to the bcr-abl tyrosine kinase expressed in CML, on a different tumor, the gastrointestinal stromal tumor (GIST), resulted in marked antitumor activity and eventually led to marketing approval in two very different specific malignancies: CML and GIST.

There are several issues, which are important to consider in the clinical development of this class of therapeutic agent.[18] These agents are theoretically less toxic than the cytotoxic agents, therefore the paradigm of dose escalation until the maximum tolerated dose may not be appropriate in these agents. Toxicity may be relatively mild, and well tolerated, as in the hematologic toxicities seen with Gleevec, which rarely resulted in the development of infections. Unusual toxicities have emerged, including edema with gleevec and pulmonary toxicities reported with Iressa. Tyrosine kinase inhibitors are theoretically cytotostatic rather than cytotoxic, so traditional response criteria may not be appropriate, although the responses seen in both indications with Gleevec are as dramatic as any seen with cytotoxics. Phase III trials using time to progression or survival may be more appropriate than tumor responses in some of these agents. Since these therapies target a specific pathway, it may be more appropriate to limit their use to patients whose tumors have been demonstrated to over express the molecular target. In the CML trial discussed in this review, accrual was limited to patients who expressed the

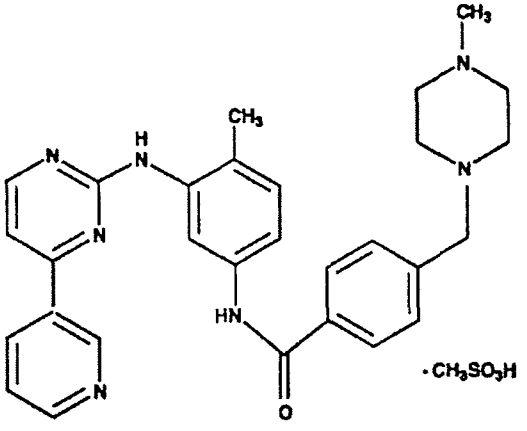
Philadelphia chromosome, which has been shown to be associated with the over expression of the bcr-able protein kinase receptor that is the target of Gleevec.

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

Gleevec is an approved product. See chemistry, pharmacology and toxicology, and clinical pharmacology reviews for NDA 21-355. The following are excerpted from the currently approved package insert:

1 CMC

Gleevec™ capsules contain imatinib mesylate equivalent to 100 mg of imatinib free base. Imatinib mesylate is designated chemically as 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate and its structural formula is



Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline powder. Its molecular formula is $C_{29}H_{31}N_7O \cdot CH_4SO_3$ and its relative molecular mass is 589.7. Imatinib mesylate is very soluble in water and soluble in aqueous buffers ≤ pH 5.5 but is very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol and ethanol, but is insoluble in n-octanol, acetone and acetonitrile.

2 CLINICAL PHARMACOLOGY

2.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Positive genotoxic effects were obtained for imatinib in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of metabolic activation. Two intermediates of the manufacturing process, which are also present in

the final product, are positive for mutagenesis in the Ames assay. One of these intermediates was also positive in the mouse lymphoma assay. Imatinib was not genotoxic when tested in an *in vitro* bacterial cell assay (Ames test), an *in vitro* mammalian cell assay (mouse lymphoma) and an *in vivo* rat micronucleus assay.

In a study of fertility, in male rats dosed for 70 days prior to mating, testicular and epididymal weights and percent motile sperm were decreased at 60 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day, based on body surface area. This was not seen at doses ≤20 mg/kg (one-fourth the maximum human dose of 800 mg). When female rats were dosed 14 days prior to mating and through to gestational day 6, there was no effect on mating or on number of pregnant females. At a dose of 60 mg/kg (approximately equal to the human dose of 800 mg), female rats had significant post-implantation fetal loss and a reduced number of live fetuses. This was not seen at doses ≤20 mg/kg (one-fourth the maximum human dose of 800 mg).

In an oral pre- and postnatal development study in rats, red vaginal discharge was noted in the 45mg kg/day group on either day 14 or 15 of gestation. At the same dose, the number of stillborn pups as well as those dying between postpartum days 0 and 4 was increased. In the F_1 offspring, at the same dose level, mean body weights were reduced from birth until terminal sacrifice and the number of litters achieving criterion for preputial separation was slightly decreased. F_1 fertility was not affected while an increased number of resorptions and a decreased number of viable fetuses was noted at 45 mg/kg/day. The NTEL for both the maternal animals and the F_1 generation was 15 mg/kg/day (one-fourth the maximum human dose of 800 mg.

Carcinogenicity studies have not been performed with imatinib mesylate.

2.2. Pregnancy

It is not known whether imatinib mesylate or its metabolites are excreted in human milk. However, in lactating female rats administered 100 mg/kg, a dose approximately equal to the maximum clinical dose of 800 mg/day based on body surface area, imatinib and its metabolites were extensively excreted in milk. It is estimated that approximately 1.5% of a maternal dose is excreted into milk, which is equivalent to a dose to the infant of 30% the maternal dose per unit body weight. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breastfeeding while taking Gleevec.

2.3. Drug Interactions

Drugs that may **increase** imatinib plasma concentrations:

Caution is recommended when administering Gleevec with inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin). Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib when Gleevec is co-administered with ketoconazole (CYP3A4 inhibitor).

Drugs that may **decrease** imatinib plasma concentrations:

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or St. John's Wort) may significantly reduce exposure to Gleevec. Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold, which significantly ($p<0.05$) decreased mean C_{max} and $AUC_{(0-\infty)}$. In patients where rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

3 Statistical Evaluation of Collective Evidence (From FDA Statistical review)

Gleevec is proposed to be used as first-line therapy in patients with Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) in chronic phase. For approval, the applicant submitted an interim report for CSTI571 0106. Study CSTI571 0106 was a randomized, open-label, multicenter, phase III study comparing the experimental treatment of Gleevec (STI571; Imatinib for injection) with the active-control (standard therapy) of Interferon-α (IFN) combined with Cytarabine (Ara-C) in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP). One thousand one hundred six (1106) patients at 177 centers in 16 countries were evenly randomized to the two arms.

The rate of major cytogenetic response was higher for the Gleevec arm than for the IFN+Ara-C arm with the results reaching statistical significance. For those patients on the Gleevec arm 82.6% (457/553) had a major cytogenetic response compared to 39.8% (220/553) on the IFN+Ara-C arm. The results were quite highly statistically significant favoring the Gleevec arm. Many of the major cytogenetic responses in the IFN+Ara-C arm occurred after crossing over to Gleevec. Up to crossover to therapy to the other arm, there were 82.6% (457/553) major cytogenetic responses on Gleevec compared to 20.2% (112/553) major cytogenetic responses on IFN+Ara-C. Patients were to receive the randomized therapy until there was no evidence of lack of response, disease progression or intolerance. Patients could have been offered the possibility of receiving the therapy of the other arm for any of the following: loss of complete hematological response (CHR), loss of major cytogenetic response (MCyR), increasing white blood cell count, intolerance of treatment, failure to achieve a CHR by 12 months, or failure to receive a MCyR by 12 months.

The primary endpoint for full approval is TTP. At the time of analysis, there were 24 and 103 events of progression respectively for the Gleevec and IFN+Ara-C arms. The results were quite highly statistically significant favoring the Gleevec arm with an estimated Gleevec vs. IFN+Ara-C hazard ratio of 0.183 (95% C.I. of (0.117, 0.285)). It is rather unlikely that a non-significant result will occur at the time of final analysis of TTP.

4 Human Pharmacokinetics and Pharmacodynamics

4.1. Pharmacokinetics

The pharmacokinetics of Gleevec™ (imatinib mesylate) have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 900 patients. Gleevec is well absorbed after oral administration with C_{max} achieved within 2-4 hours post-dose. Mean absolute bioavailability for the capsule formulation is 98%. Following oral administration in healthy volunteers, the elimination half-lives of Gleevec and its major active metabolite, the N-desmethyl derivative, were approximately 18 and 40 hours, respectively. Mean AUC increased proportionally with increasing dose in the range 25 mg - 1000 mg. There was no significant change in the pharmacokinetics on repeated dosing, and accumulation is 1.5-2.5 fold at steady state when Gleevec is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *vitro* experiments is approximately 95%, mostly to albumin and α_1-acid glycoprotein.

Metabolism and Elimination

CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows *in vitro* potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for imatinib.

Elimination is predominately in the feces, mostly as metabolites. Based on the recovery of compound(s) after an oral ^{14}C-labeled dose of imatinib, approximately 81% of the dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

Typically, clearance of imatinib in a 50-year-old patient weighing 50 kg is expected to be 8 L/h, while for a 50-year-old patient weighing 100 kg the clearance will increase to 14 L/h. However, the inter-patient variability of 40% in clearance does not warrant initial dose adjustment based on body weight and/or age but indicates the need for close monitoring for treatment related toxicity.

4.2. Pharmacodynamics

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. In colony formation assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows inhibition of Bcr-Abl positive colonies from CML patients.

In vivo, it inhibits tumor growth of Bcr-Abl transfected murine myeloid cells as well as Bcr-Abl positive leukemia lines derived from CML patients in blast crisis.

Imatinib is also an 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. *In vitro*, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating c-kit mutation.

IV Description of Clinical Data and Sources

1 Overall Data

The primary source for this sNDA review consisted of data submitted to the sNDA on study 106. Additional information was gained from the data submitted with the original NDA 21-344, and literature sources cited in the footnotes.

2 Tables Listing the Gleevec Clinical Trials in CML

Table 2 lists the registration trials for Gleevec in CML.

Table 4: Gleevec clinical trials in CML

Study Number	Indication	Phase	Patient exposure
1	Dose finding	1	83
102	CML Blast crisis	2	260
106	**Untreated CML**	**3**	**553**
109	CML accelerated phase	2	235
110	CML chronic refractory to Interferon	2	532

A total of 1663 patients with CML were exposed to Gleevec in five registration trials.

3 Postmarketing Experience

Gleevec was approved on May 10, 2001. As of November 11, 2002, postmarketing surveillance has received 818 adverse event reports, including duplicates.

Table 5: Most common adverse events (>5%) reported to FDA (N= 818)

Preferred term	N	% of total
Pyrexia	106	13
Pancytopenia	75	9.2
Nausea	63	7.7
Thrombocytopenia	58	7.1
Vomiting	54	6.6
Neutropenia	49	6.0
Dyspnea NOS	45	5.5
Oedema NOS	43	5.3
Pneumonia NOS	43	5.0

(Including duplicates)

In addition, there were 59 reports of renal failure or impairment; including 14 reports of dialysis. There were 91 reports of bilirubin or transaminase abnormalities, 15 reports of hepatotoxicity, and 6 reports of hepatic failure. There were 26 reports of sepsis and 5 reports of shock. There were 18 reports of rash, 17 reports of erythema multiforme, and 7 reports each of Stevens Johnson syndrome and toxicoderma. There were 118 reports of various types of edema, including 4 reports of cerebral edema and 4 reports of papilledema. Clearly this drug causes renal and hepatic toxicity in a minority of patients, rash and edema is fairly common, and severe skin reactions and cerebral edema have been reported. A review is currently in progress to eliminate duplicate reports and to identify emerging patterns of adverse events.

4 Literature Review

The sponsor performed an extensive review of the literature of treatment of CML, and provided copies of these references. The FDA medical reviewer performed an additional literature review with attention to the more recent publications about CML. The references cited are listed at the end of the NDA review. The sponsor's literature review appears to be adequate.

V Clinical Review Methods

1 How the Review was Conducted

This review focused on the data submitted for study 106, in an untreated Philadelphia-chromosome positive CML population. Data were analyzed in order to confirm the primary endpoint of superiority in time to progression and the secondary endpoints of hematotolgic and cytogenetic responses, as well as progression to accelerated phase and blast crisis. Dr John Johnson, medical team leader, performed the safety review, and these reviews were combined. A

consultation was obtained from the Division of Scientific investigation and the site that contributed the most patients to the study in the US was inspected. A separate statistical review was performed.

2 Overview of Materials Consulted in Review

Data submitted under sNDA 21-355 including primary datasets on all individual patients, study reports, case report forms, and communications with the sponsor. In addition, the literature was reviewed, and the review findings were discussed with 2 members of the Oncology Drugs Advisory Board (ODAC).

3 Overview of Methods Used to Evaluate Data Quality and Integrity

The primary data were analyzed for consistency with the study reports and individual patient data printouts. Selected case report forms (CRF's) were also reviewed. Response rates were analyzed with respect to clinical study center for inconsistencies, and the Division of scientific Investigation was consulted to inspect the study site that contributed the most patients. The FDA DSI investigator examined the case report forms and compared them with source documents such as patients' charts to verify their accuracy.

4 Were Trials Conducted in Accordance with Accepted Ethical Standards

This sponsor has asserted that the study was performed in accordance with standard operating procedures designed to ensure adherence to good clinical practice guidelines and ensure the ethical protection of the patients, as required by the following directives in operation at the time:

1. Declaration of Helsinki, concerning medical research in humans ('Recommendations Guiding Physicians in Biomedical Research Involving Human Patients', Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, 1996).
2. Directive 91/507/EEC: The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies, parts 50 and 56, concerning Informed Patient Consent and IRB approval.

5 Evaluation of Financial Disclosure

Standard processes, i.e. FDA forms 3454 and 3455, were used to obtain disclosable information. Letters requesting information were sent out on several occasions and payments were often delayed until information was provided. Information obtained indicated the following:

- No principal or sub-investigators were full or part-time Novartis employees.
- Dr. —— . study 0106 (center136 –Switzerland) declared that he had received unspecified payments from Novartis exceeding ——
- Dr . —— (center 77 - US) declared that he had in excess of —— worth of ——
- All but 2 out of 178 investigators returned the financial disclosure forms.

Conclusion

Based on the above it does not seem likely that individuals who have disclosable financial interests and those two who did not provide financial disclosure information could have significantly biased study results.

VI Integrated Review of Efficacy

1 Brief Statement of Conclusions

Study 106 was an open-label randomized parallel-group study of Gleevec versus versus Interferon-α (IFN-α) combined with Cytarabine in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase. The primary efficacy endpoint was progression free survival, the secondary efficacy endpoints were time to accelerated phase and blast crisis, complete hematologic response, and major and complete cytogenetic response and patient reported quality of life and survival. Treatment arms appeared to be well balanced with respect to important prognostic characteristics. The study was well conducted, and only two percent of patients on the Gleevec arm and five percent of patients on the interferon arm were excluded from the per protocol analysis for major protocol violations. However, forty percent of patients on the interferon were allowed to cross over to the Gleevec arm, compared with 1.3% of patients on Gleevec who crossed over to the interferon arm. This complicated the interpretation of the efficacy results. The most common reason for crossover from interferon to Gleevec was for intolerance to treatment. There were imbalances between treatment arms in terms of protocol violations, dropouts, treatment received, and dose intensity. These imbalances resulted in patients on the Gleevec

treatment arm receiving close to 100% of the planned dose intensity, and patients on the interferon arm receiving only 56% of the planned dose intensity.

The analysis of the primary efficacy endpoint, progression free survival, was performed early because of highly significant results at interim analysis of the cytogenetic response rates. There were 127 progression events. The TTP results are quite highly statistically significant, with a hazard ratio for progression of 0.183 (95% C.I. of 0.117, 0.285) of treatment with Gleevec compared with that of interferon. The difference was highly statistically significant by log-rank test. The analysis of secondary efficacy endpoints, including time to accelerated phase and blast crisis, complete hematologic response, major and complete cytogenetic response and patient reported quality of life are all statistically significant favoring the Gleevec arm. Survival was not significantly different between arms, however the median survival will not be reached for 7-10 years. Patient reported effects of toxicity were stable on the Gleevec arm and decreased on the interferon treatment arm, consistent with more symptoms of toxicity on interferon.

Despite imbalances in the dose intensity, and extensive crossover from interferon to Gleevec treatment arms, the treatment of patients with CML in chronic phase with Gleevec appears to be significantly superior to the treatment of CML patients in chronic with interferon in all efficacy endpoints except for survival. The durability of these endpoints and the effects on survival have yet to be demonstrated.

2 General Approach to Review of the Efficacy of the Drug

This review focused on the supplemental NDA data submitted for Novartis CSTI571 study 106 including information on 1106 recently diagnosed patients with Philadelphia-chromosome positive CML in chronic phase.

3 Detailed Review of Trials by Indication

3.1. Study No: CSTI571 0106:

Title: A phase III study of STI 571 versus Interferon-α (IFN-α) combined with Cytarabine in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP).

Reviewer comment: Since the protocol specified STI 571 as the study drug and the protocol was study number CSTI571 0106, also referred to as the "IRIS study:" International Randomized Study of IFN + Ara-C vs STI571, Gleevec will be referred to as STI 571 in the following description of the protocol.

3.2. Initial Primary Objective:

To determine the time-to-treatment failure in adult patients with newly diagnosed previously untreated Ph+ CML-CP randomized to STI 571 compared to patients randomized to IFN-α Cytarabine.

3.3. Amended Primary Objective

After being informed by the FDA that time to treatment failure (TTF) was unacceptable for registration, amendment 2 was submitted July 24, 2000, changing the primary endpoint of the study to progression free survival, (PFS).

Progression was defined as:

- Death
- Accelerated phase, blast crisis,
- Loss of CHR or MCR
- Increasing WBC counts in patients who did not achieve CHR

These are further defined in efficacy parameters (section IV of this review)

Reviewer comment: in a meeting on May 3, 2000, the FDA recommended either time to onset of accelerated phase or blast crisis or survival should be the primary efficacy endpoints of study 0106 to be used as the basis of full marketing approval. Time to treatment failure (TTF) was initially proposed as the primary objective of this study, but TTF is a composite endpoint of efficacy and toxicity and not acceptable as an endpoint for registration. Intolerance to treatment (inability to take the drug) cannot be an efficacy endpoint. (See regulatory background)

3.4. Secondary objectives

- To determine the rate and duration of complete hematological response (CHR) in patients randomized to ST1571 compared to patients randomized to IFN-a + Cytarabine.
- To determine the rate and duration of major cytogenetic response (MCR) in patients randomized to STI 571 compared to patients randomized to IFN-a+ Cytarabine.
- To determine the rate and duration of MCR and of CHR attributable to crossover therapy in patients who cross over to STI 571 or to IFN-a + Cytarabine.
- To determine overall survival of patients randomized to STI 571 as compared to patients randomized to IFN-a+ Cytarabine.
- To determine the tolerability and safety of STI 571 compared to IFN-α + Cytarabine.
- To evaluate quality of life (QOL), and disease and treatment related toxicities in patients randomized to STI 571 compared to patients randomized to IFN-α+ Cytarabine.
- To evaluate healthcare resource utilization (RU).

- To evaluate the population pharmacokinetics of ST1571.

- To perform pharmcogenomics evaluations to study in an exploratory fashion RNA expression and DNA polymorphisms, (eg bcr-abl and c-Kit) in tumor cells in the blood and bone marrow in this patient population.

Reviewer comment: Hematologic and cytogenetic response rates provided the surrogate basis for registration in the second line CML indication, but these were not acceptable for registration in the first line CML indication because these have not been shown to predict improved survival in well-controlled randomized clinical trials. Failure to achieve a CHR at 6 months or a Major Cytogenetic Response (MCyR) at 12 months also were not considered by the FDA to be acceptable efficacy endpoint. Superiority of survival if demonstrated will provide the basis for registration in the first line indication. Global QOL endpoints have not been accepted by the FDA as the basis for registration. These analyses were considered to be exploratory.

3.5. Study design

3.5.1 Patient Population

- Demographics: Male or female patients between 18 and 70 years

- Diagnosis of chronic myelogenous leukemia and fulfill all of the following criteria:

  - Within 6 months of initial diagnosis of CML-CP (date of first cytogenetic analysis).
  - Previously untreated for CML with the exception of hydroxyurea,
  - Cytogenetic confirmation of Philadelphia chromosome
  - No evidence of accelerated phase or blast phase:
    - < 15% blasts in peripheral blood and bone marrow;
    - < 30% blasts plus promyelocytes in peripheral blood and bone marrow;
    - < 20% basophils in peripheral blood,
  - No evidence of extramedullary leukemic involvement, (excepting the spleen and liver)

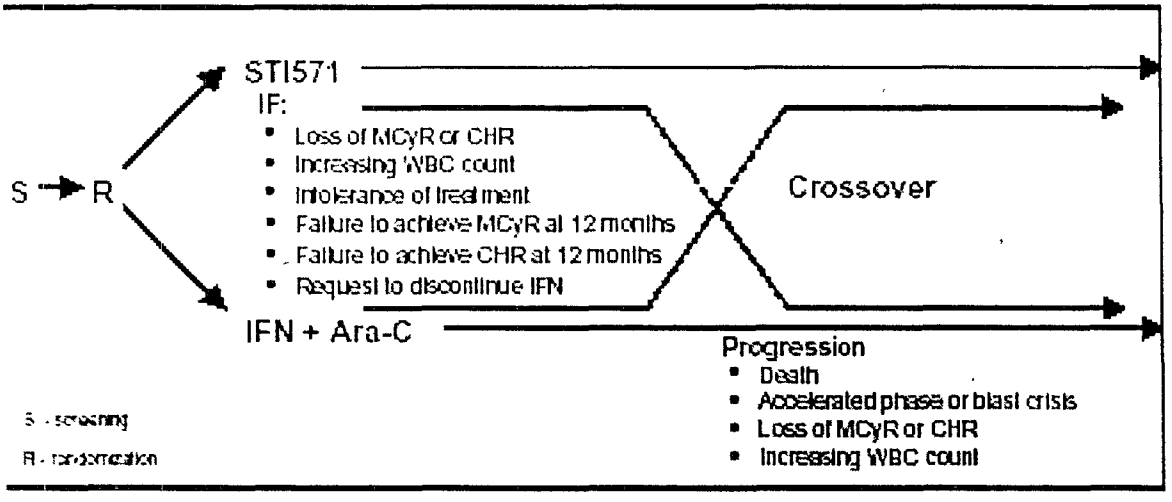
3.5.2 Exclusion criteria

  - Patients who have received other investigational agents
  - Prior chemotherapy, including regimens used in peripheral blood progenitor cells (PBPCs) mobilization for hematopoietic progenitor-cell transplantation. (Previous treatment with hydroxyurea is allowed.)
  - Patients with identified sibling donors where allogeneic hone marrow transplant is elected as first line treatment.
  - ECOG Performance Status Score > 3.
  - Serum bilirubin, SGOT, SGPT, or creatinine concentrations > 1.5 x the institutional upper limit of the normal range (IULN).
  - International normalized ratio (INR) or partial thromboplastin time (PTT) > 1.5 x IULN
  - Uncontrolled medical disease such as diabetes mellitus, thyroid dysfunction, neuropsychiatric disorders, infection, angina, or Grade 3/4 cardiac problems as defined by the New York Heart Association Criteria.

- Known positivity for human immunodeficiency virus (HIU) (baseline testing for HIV is not required.)
- Major surgery within 4 weeks of Study Day 1, or who have not recovered from prior major surgery.
- Pregnant, breast feeding, of childbearing potential without a negative pregnancy test prior to Study Day 1, and male or female of childbearing potential unwilling to use barrier contraceptive precautions throughout the trial (postmenopausal women must be amenorrheic for at least 12 months to he considered of non-childbearing potential).
- History of another malignancy within the past five years, with the exception of basal cell skin carcinoma or cervical carcinoma in situ.
- History of non-compliance to medical regimens or who are considered potentially unreliable.

Reviewer comment: The eligibility criteria were similar to that reported by Guilhot, et. al. in their study of IFN and Cytarabine in untreated patients with CML. Allogeneic bone marrow transplant is potentially curative in this disease, therefore patients planning to go on to transplant were excluded, however patients with the potential to go on to transplant were not excluded. An imbalance in the numbers of patients in either arm going on to transplant might affect results.

Figure 1 Study outline (Randomization, crossover)



3.5.3 Treatment plan:

The trial was open label, parallel group, multicenter, multinational study conducted in 1106 patients with newly diagnosed Philadelphia chromosome-positive CML.

3.5.4 Treatment assignment

A central telephone randomization site randomized patients, no prognostic stratification factors were used.

3.5.5 Screening Assessment

Laboratory screening assessments and physical examination including performance status, vital signs, weight and BSA should be performed within 1 week prior to randomization. The bone marrow aspirate must be performed within 4 weeks prior to randomization.

3.6. Gleevec (STI 571) treatment arm:

3.6.1 Dose and schedule:

Gleevec (STI 571) was to be administered orally at a starting dose of 400 mg q.d. and be prepared and dispensed by the investigator or pharmacist at each center. Patients may be dispensed up to a 30-day supply of medication. After the first 6 months of therapy STI 571 may be dispensed for up to a 3-month period if appropriate.

3.6.2 Dose escalation plan for STI571 (Gleevec)

3.6.2.1 Initial

For patients who fail to achieve either a complete hematologic response at 3 months or a major cytogenetic response at 12 months, the STI 571 dose will be escalated to 400 mg bid in the absence of dose limiting toxicities as described above.

3.6.2.2 Amended

Amendment 1 dated 7/24/200 the protocol was changed to allow dose escalation of STI 571 to be performed step wise from 400 mg qd to 600 mg qd and then to 400 mg bid.

1. Dose escalate from 400 mg/day to 600 mg/day administered once per day;
2. if no > grade 2 toxicity occurs during the initial 4 weeks the dose of STI 571 may be further increased to 800 mg/day administered as 400 mg twice per day

3.6.3 Dose Reduction guidelines for STI-571 (Gleevec)

3.6.3.1 Grade 2 Non-Hematological Toxicity

- If a patient experiences a Grade 2 non-hematologic toxicity that does not resolve despite therapeutic intervention, STI 571 must be withheld until the toxicity has resolved to < Grade 1
- ST1571 may then be resumed at a dose of 400 mg daily.
- If the Grade 2 toxicity recurs, STI 571 must be withheld until the toxicity has resolved to < Grade 1, and the dose must be reduced to 300 mg daily.

3.6.3.2 Grade 3-4 Non-Hematological toxicity

- If a patient experiences > grade 3 non-hematological toxicity STI571 must be withheld until the toxicity has resolved to < Grade 1. STI 571 may then be continued at a reduced dose of 300 mg daily.