

Complete hematologic response (CHR) Studies 0102 and 0109:

<5% blasts in BM
No blasts in PB
ANC >1.5 x 10⁹/L and Platelets >100 x 10⁹/L
No extramedullary involvement

No evidence of leukemia (NEL):

As for CHR, but without complete recovery of peripheral blood,
i.e. 1.0 ANC < 1.5 x 10⁹/L and 2.0 Platelets < 100 x 10⁹/L

Return to chronic phase (RTC):

< 15% blasts in PB and BM
< 30% blasts+promyelocytes in PB and BM
< 20% basophils in PB
No extramedullary involvement other than spleen or liver

Complete hematologic response (CHR) Study 0110

WBC <10 x10⁹/L
Myelocytes + metamyelocytes <5% in PB
No blasts + promyelocytes in PB
< 20% basophils in PB
No extramedullary involvement

Cytogenetic response

Based on % positive cells = (positive cells / examined cells) x 100, at each bone marrow assessment the cytogenetic response was either:

- Complete: 0% Ph+ cells
- Partial: >0 - 35 % Ph+ cells
- Minor: >35 - 65 % Ph+ cells
- Minimal: >65 - 95 % Ph+ cells
- None: >95 % Ph+ cells
- Not done: <20 metaphases were examined and/or response could not be assigned

A bone marrow sample was to be considered as assessable for cytogenetic response only if it contained 20 metaphases. This condition was always maintained for affirmation of complete response. However, an assessment of partial response was retained in a sample with <20 metaphases when it was immediately preceded or followed by a complete or partial response in another sample.

Duration of major cytogenetic response=

This duration was evaluated for all patients with major cytogenetic response and was defined as the time between first documented complete or partial response and the earliest of the following:

- loss of complete cytogenetic response- increase to >0% Ph+ cells.
- loss of partial cytogenetic response -increase by 30% Ph+ cells compared to lowest value before current assessment or an increase to 65% Ph+ cells
- discontinuation due to unsatisfactory therapeutic effect or death.

Patients still on study at the date of cut-off were censored at the time of their last bone marrow evaluation for cytogenetics, as long as there was no evidence of loss of major cytogenetic response. Patients discontinuing were censored at the time of the last bone marrow evaluation if the discontinuation was for reasons other than unsatisfactory therapeutic effect or death.

Time to complete or major cytogenetic response-

Time to cytogenetic response was defined for all patients with complete or major cytogenetic response as the time until first documented complete (or major) cytogenetic response.

Time to event analyses have been made in which duration = (end date - start date) +1. If not mentioned otherwise, durations were censored at the last examination date, when patients were still on study without evidence of progression (and/or loss of response) or patients discontinued due to reasons other than unsatisfactory therapeutic effect or death. The last examination date was defined as last date of either visit date, LAB, BM, EMD or dosage information. For a patient discontinuing study medication, the date of last dose of study medication was taken as the last examination date unless death was the reason for discontinuation in which case the date of death was taken as the last examination date.

The time to event variables were calculated using the calculated confirmed complete hematologic response and were defined as follows:

Time to complete hematologic response-

This was defined for all patients with calculated confirmed complete hematologic response as the time until first documented response (which was confirmed 4 weeks later). This variable was not specified in the protocol but was calculated as additional analysis.

Duration of complete hematologic response-

This duration was evaluated for all patients with calculated confirmed complete hematologic response and was defined as the time between first documented response (which was confirmed 4 weeks later) and the earliest date of the following

- loss of response (WBC >20 x 10⁹/L or when any of the other criteria for complete hematologic response were no longer fulfilled).
- progression to blast crisis or accelerated phase
- discontinuation due to unsatisfactory therapeutic effect or death.

6.0 Study 102 Ph-positive CML in myeloid blast crisis.

This was a Phase II multi-center, open-label, single-arm, non-randomized study of CML patients, either untreated or previously treated for blast crisis, who received STI571 as a single agent at an initial dose of 400 mg/day which was allowed to increase to 600 mg/day (amendment 1, 06 October 1999). There was a further possibility of escalating up to 800mg/d based on the phase I study findings showing acceptable safety up until these doses and promising efficacy findings.

Patients enrolled after Amendment 2 (21 Dec 1999), received once daily oral STI571 at a dose of 600 mg for 24 weeks. After completing 24 weeks of therapy, patients were eligible to receive additional therapy during Part 2 of the trial if, in the opinion of the investigator, the patient had benefited from treatment with STI571 and there were no safety concerns. During Part 2 (which was of indefinite duration), patients continued to receive STI571 on a daily basis until either death, the development of unacceptable toxicity or a decision to withdraw therapy as no longer beneficial, etc. The frequency of visits was reduced in Part 2. Patients who discontinued study drug prior to death were followed for survival. The third amendment to the protocol (30 Aug 2000) allowed STI571 to be taken with food in order to limit the gastric side-effects, no significant food interaction having been shown in a pharmacokinetic study.

This analysis and report is based on a cut-off date (2 October 2000) for data accrual. This date corresponds to 3 months after recruitment of the last patient.

6.1 Study objectives

Primary

- To determine the rate of hematologic response (confirmed after 4 weeks) in adult patients with Ph chromosome-positive CML who are in myeloid blast crisis.

Secondary objectives

- To determine the duration of hematologic response.
- To evaluate overall survival.
- To evaluate cytogenetic responses.
- To evaluate the safety profile of STI571.
- To evaluate improvement of symptomatic parameters.
- To study the pharmacokinetic profile of STI571 in a sub-group of patients.
- To study possible mechanisms involved in resistance to STI571 and to confirm signal transduction inhibition in vivo.

6.2 Inclusion and exclusion criteria

Inclusion criteria

- Male or female patients Ph chromosome-positive CML who are in myeloid blast crisis 18 years of age. Some investigators evaluated Bcr-Abl genotype positivity by fluorescent in situ hybridization (FISH). FISH positivity was accepted as evidence of compliance with the inclusion criterion of Ph chromosome positivity in the absence of a positive karyotype.
- Patients with Ph chromosome-positive CML in myeloid blast crisis defined as either:
30% blasts in peripheral blood and/or bone marrow
- by flow cytometry criteria. Patients will be regarded as having myeloid blast crisis if they fail to meet the following criteria. The diagnosis will be confirmed subsequently by a centralized review procedure.
 - B- or T-lymphoid blast crisis CML (myeloperoxidase negativity and
 - presence of at least 2 lymphoid markers, with no more than 2 myeloid markers

Core antigens for flow cytometry

Lineage	Marker
T cell	CD2, CD7, CD3
B-cell and pre B cell	CD19, CD10, CD20, CD79a Kappa, Lambda
Myeloid	CD13, CD14, CD33
Stem cell	CD34, TdT

- Newly diagnosed CML blast crisis patients and patients with CML blast crisis who had received prior therapy for accelerated or blastic phases are eligible. To be categorized as "newly diagnosed", patients with CML in blast crisis were not to have received specific therapy for CML accelerated or blast phases, with the exception of interferon-alpha or hydroxyurea. Patients must have recovered from side effects of prior therapy.
- ECOG P.S. ≤ 3
- SGOT and SGPT not more than 3 times the upper limit of the normal range (ULN) (or not more than 5 times the ULN if clinically suspected leukemic involvement of the liver). Total serum bilirubin level not more than 3 times the ULN at the laboratory where the analyses were performed.
- Serum creatinine concentration not more than 2 times the ULN where the analyses were performed.
- A negative pregnancy test in patients of childbearing potential
- Written voluntary informed consent

Exclusion criteria

- Patients previously treated for blast crisis were not to have received any of the following with respect to Day 1 of the study: busulfan within six weeks, interferon-alpha within 48-hours, hydroxyurea within 24-hours, homoharringtonine within 14

days, low-dose, moderate dose or high dose cytosine arabinoside within 7, 14 and 28 days respectively, anthracyclines, mitoxantrone, or etoposide within 21 days.

- Patients receiving any hematopoietic stem cell transplantation within 6 weeks of Day 1
- Patients receiving any other investigational agents within 28 days of Day 1.
- Patients with Grade 3/4 cardiac disease or any other serious concurrent medical conditions.

6.3 Protocol amendments

Three amendments were made to the protocol.

Protocol Amendment 01 (dated 06-Oct-99)

- Enrollment of patients with advanced Ph chromosome-positive leukemias in this Phase II study was temporarily placed on hold while dose-escalation and efficacy follow-up in this patient population continued in the Phase I study. The decision to re-open recruitment into this present study was to be based on the additional results observed in the Phase I trial.
- However, a limited number of patients (n=37) had already been enrolled into the trial and this amendment modified some of the treatment procedures to be followed.
- Intra-patient dose escalations from 400 to 600 mg in patients who had no response or had a relapse following an initial response were allowed.
- Patients with serum bilirubin levels not more than 3.0 x ULN were allowed to enter the study.
- Patients could be followed at the referral center following a minimum period of two months of follow-up at the study center.
- Fluorescence in situ hybridization (FISH) analysis was to be performed on bone marrow samples whenever the number of metaphases identified for cytogenetics was below 20.

Protocol Amendment 02 (dated 21-Dec-99)

- The decision to reactivate the protocol was supported by additional follow-up efficacy and safety data obtained in patients treated in the phase I trial (Study 03 001) and the distinction between patients having received prior treatment for accelerated phase or blast crisis of CML and patients not having received such treatment (newly diagnosed) was introduced. The main points of the amendment were:
- Preferential recruitment of patients not previously treated for accelerated phase or blast crisis (no antineoplastic therapy except hydroxyurea or interferon).
- The initial dosage became 600 mg/day
- The statistical section of the protocol was also revised. Statistical considerations including target hematologic response rate was now based on the newly diagnosed myeloid blast crisis CML patient population who had not received

previous therapy for the accelerated and blastic phases of their disease. The sample size calculation in this patient group was adjusted by increasing the power from 80% to 90%. Previously treated patients were to be studied in an exploratory fashion. The sample population was increased to 150 patients of whom 100 were to be "newly-diagnosed" (i.e. "previously-untreated").

- Patients who progressed while on STI571 treatment at a dose of 600 mg/day could have the dose increased to 800 mg, administered as 400 mg twice daily.
- Patients receiving therapy with drugs known to significantly modify gastric pH (e.g. H2blockers, proton pump inhibitors) were permitted to enter the study. This previous exclusion criterion was lifted so as to harmonize selection criteria across all three phase 11 studies after anecdotal evidence had been obtained suggesting that addition of such drugs need not alter the quality of response once obtained.
- Pre- and post-treatment blood samples were to be collected in order to study prospectively eventual mechanisms of drug resistance to STI571.
- A blood sample was to be collected at the time of disease progression for the measurement of STI571 concentration, to exclude pharmacokinetic factors contributing to relapse.
- Blood sampling schedule for the full pharmacokinetic profile was prolonged to up to 72 hours by adding two time points.
- Procedures for the management of Grade 4 neutropenia were modified by increasing the duration of neutropenia required before bone marrow examination; allowing a minimum of 4 weeks before dosage reduction; allowing continuous treatment with STI571 after dosage reduction.
- The dose reduction steps for non-hematologic toxicity were simplified.
- Blood samples were to be collected to measure the concentration of α -1-acid glycoprotein. STI571 binds to α -1-acid glycoprotein, which is elevated in patients with malignancies. The aim was to investigate whether the concentration of α -1-acid glycoprotein changes over the STI571 treatment period and ultimately correlates with clinical outcome. The results of this will be reported separately.

Protocol Amendment 3 (30 August 2000)

- The purpose of this amendment was to allow STI571 to be administered during meals, following results from a preliminary study that showed minimal effects of food on the bioavailability of STI571.
- The supply of STI571 to patients was changed to allow monthly supply during Part 1 and 3-monthly supply for the first 6 months of Part 2 of the study, and thereafter 4-monthly supply.
- Other changes in study conduct
 - An internal GCP audit of Italian center number 7 revealed some unauthorized procedures contrary to GCP. For his own research purposes, the investigator performed an unapproved/unauthorized PK study on 4 patients from whom blood samples were taken to measure STI571 plasma concentrations in the presence or absence of the antibiotic, Dalacin (Clindamycin) administered iv at high doses. Novartis instructed the investigator to stop these unapproved studies and reminded him of his commitments to follow GCP, obtain Ethics Committee approval and patient informed consent.

6.4 Statistical methods

Populations

Intent-to-treat (ITT) population consists of all enrolled patients. The **safety population** consists of all patients who received at least one dose of study medication. As all patients enrolled were also treated the ITT and Safety populations are identical.

For the analysis of efficacy, following a recommendation from the FDA, patients have been subgrouped according to whether or not they had received previous antineoplastic treatment for their blast crisis. Investigators were asked to indicate in the CRF for all prior antineoplastic therapies whether it was given for the treatment of accelerated phase or blast crisis. On the basis of this information, patients were assigned in the analysis to the different sub-categories as follows:

— **patients considered as untreated (newly diagnosed)** patients for whom either no treatment was recorded for accelerated phase or blast crisis, or for whom the only treatment recorded for accelerated phase or blast crisis included interferon, hydroxyurea, low dose Ara-C which were considered as only palliative for the treatment of advanced stage CML.

patients considered pretreated all the patients noted with other previous antineoplastic drug treatment specifically given for accelerated phase and blast crisis (by the investigator) including drugs such as high-dose Ara-C, mitoxantrone, etoposide (VP-16), daunorubicin, adriamycin, decytabine. Patients having had a BMT for advanced phase were included in this category.

Per protocol (PP) population is a subset of the ITT population without major violations of the protocol (i.e. violations likely to significantly compromise the design of the study as regards the assessment of the drug's efficacy in patients at this phase of the disease).

Major protocol violations taken as disqualifying patients from the per protocol populations were as follows:

- **for hematologic and cytogenetic response assessments**
 - patients not in the defined phase of CML as defined in the protocol
 - documented Ph chromosome negativity
 - administration of prescribed antineoplastic drugs during treatment with STI571 (hydroxyurea for more than one week or Ara-C, interferon, busulfan, etoposide, anthracyclines, mitoxantrone).

- **for hematologic response assessment only**
 - absence of two post-baseline efficacy assessments at least 4 weeks apart in patients not dying or discontinuing treatment because of treatment failure (adverse event or abnormal laboratory value, unsatisfactory therapeutic effect)
- **for cytogenetic response assessment only**
 - absence of at least one post-baseline bone marrow cytogenetics in patients not dying or discontinuing treatment because of treatment failure (adverse event or abnormal laboratory value, unsatisfactory therapeutic effect)
 - 20 metaphases.

Cancer-related symptoms and ECOG performance status

Significant cancer-related symptoms (fever, night sweats, bone pain, abdominal discomfort, arthralgia) present prior to the start of study drug were included on the Cancer-Related Symptoms CRF. Cancer-related symptoms were also evaluated after 12 weeks (3 month analysis) and 24 weeks (6 month analysis). At any time throughout the study should the severity grade have worsened, the symptom was transcribed onto the Adverse Event CRF.

Similarly, ECOG performance status was recorded at baseline and monthly during the study.

Overall survival

To evaluate overall survival, all patients were followed after the last dose of study drug every month for the first three months and thereafter every three months until death.

Safety assessments

Safety assessments consisted of monitoring and recording all adverse events (with their severity and relationship to study drug), the regular monitoring of hematology and biochemistry at the study centers' local laboratories, physical examinations, measurement of vital signs and documentation of all concomitant medications and/or therapies.

Hematology parameters included: hemoglobin, WBC, platelets, blood differentials in % (neutrophils, lymphocytes, monocytes, basophils, eosinophils, blasts, early forms, and other forms). Absolute neutrophils were calculated using the % differential of WBC.

Biochemistry parameters included: SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, creatinine, BUN or urea, albumin, total protein, uric acid, LDH, calcium, phosphate, sodium, and potassium.

AEs and laboratory parameter abnormalities were graded for severity using the National Cancer Institute/National Institute of Health (NCI/NIH) common toxicity criteria (CTC).

Drug levels and pharmacokinetic assessments

Basic pharmacokinetic characteristics of STI571 and its metabolite(s) were to be described. The plasma concentrations and pharmacokinetic behavior were assessed. Plasma concentrations of STI571 were determined by γ -counter at Novartis. The assays were validated with regard to precision, sensitivity, linearity, recovery, and specificity.

Blood samples

Blood samples for the measurement of the complete plasma profiles of STI571 and its metabolite(s) were to be collected from the first 20 patients enrolled at 600 mg/day (US centers only) and were actually taken from 25 patients. Blood samples were collected immediately prior to study drug administration on Day 1 and at the following time points following drug administration: 0.5, 1, 1.5, 2, 4, 8, 24 (no drug), 48 (no drug) and 72 (pre-dose) hours. Blood samples were collected immediately prior to study drug administration on Day 8 and at the following time points 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.

Sample size and power considerations

The sample size was based on Fleming's single stage, single arm procedure testing the (one-sided) hypotheses $H_0: p \leq p_0$ and $H_1: p > p_1$. This design is commonly used for Phase II studies. It specifies p_0 as the uninteresting response rate which usually is considered as the rate that does not warrant further investigation of the drug, and p_1 , as the rate which should not be missed, i.e. which if true would imply that the treatment has therapeutic efficacy. In this study, $p_0=15\%$ and $p_1=30\%$.

The acceptable probabilities of making incorrect decisions were as follows: the probability of rejecting H_0 when in fact p is no more than 15% has to be less than 2.5% (one-sided) and the probability for rejecting H_1 , when in fact p is no less than 30% has to be less than 10% (power=90%).

For the above consideration, and using binomial distribution, a minimal sample size of 79 patients was needed. The study "win criteria" were to be fulfilled when 19/79 responders were observed. To account for dropout rate, the sample size was increased to 100 untreated patients.

As the study over-recruited, the final sample size and corresponding response rates required for success were recalculated as shown in Table 7.

Table 7 Planned and actual sample size

Sample	Sample size	Overall hematologic response success criteria				
		Minimum no. of responders	po	p ₁	p	95% CI t
Planned	79 (minimum)	19	15%	30%	24.1%	15.1-35.0%
Actual	165	35	15%	30%	21.2%	15.2-28.2%

po = uninteresting response rate (=critical lower confidence limit); p₁ = response rate which should not be missed; p = response rate at which study would be successful if CI has lower limit > po; t Confidence interval (CI) using Pearson-Clopper limits

6.5 Study Results per Sponsor - Study 0102

A total of 260 patients were enrolled in this study in 27 investigative centers between 26 July 1999 (first dose 2 August 1999) and 30 June 2000 (first dose 30 June 2000).

For patients recruited between 26 July - 31 December 1999, the initial dosage was 400 mg/d. Amendment 2 changed the initial dosage to 600 mg/d for patients subsequently recruited between 6 January - 30 June 2000. Amendment 2 also resulted in the preferential selection of patients not previously treated for accelerated phase and blast crisis.

6.5.1 Patient disposition (ITT population)

The current disposition of patients entered into study 0102 is indicated in Table 8. As indicated there are 4 relevant subgroups; patients previously treated or not and patients receiving STI571 400 mg or 600 mg.

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Table 8 Patient disposition-study 0102

Disease Subgroup Initial dose(mg/d)	Untreated			Treated			TOTAL
	400 mg	600 mg	All	400 mg	600 mg	All	All doses
		N=11	N=154	N=165	N=26	N=69	N=95
N=260							
No. (%) of patients							
Starting treatment	11 (100)	154(100)	165(100)	26(100)	69(100)	95(100)	260(100)
Still on treatment ¹	2(18.2)	68(44.2)	70(42.4)	7(26.9)	16(23.2)	23(24.2)	93(35.8)
Total discontinued	9(81.8)	86(55.8)	95(57.6)	19(73.1)	53(76.8)	72(75.8)	167(64.2)
Reason for discontinuation							
Safety event ²	1 (9.1)	11 (7.1)	12(7.3)	1 (3.8)	8(11.6)	9(9.5)	21 (8.1)
Unsatisfactory therapeutic effect	6(54.5)	56(36.4)	62(37.6)	15(57.7)	36(52.2)	51 (53.7)	113(43.5)
Patient proceeded to BMT	0	7(4.5)	7(4.2)	1 (3.8)	2(2.9)	3(3.2)	10(3.8)
Protocol violation	1 (9.1)	1 (0.6)	2(1.2)	0	1 (1.4)	1 (1.1)	3(1.2)
Withdrawal of consent	0	1 (0.6)	1 (0.6)	0	1 (1.4)	1 (1.1)	2(0.8)
Death ³	1 (9.1)	10(6.5)	11 (6.7)	2(7.7)	5(7.2)	7(7.4)	18(6.9)

1. Patients still on treatment at time of cut-off (20Oct 2000)

2. Non fatal adverse events &/or laboratory abnormalities

3. Death as the reason for discontinuation. But a further 64 patients died within 28 days of discontinuation

6.5.2 Major Protocol Violations

Table 9 summarizes the numbers of patients with major protocol violations. Major violations constituted grounds for exclusion from the per-protocol analysis populations for hematologic and/or cytogenetic response assessments.

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Table 9 Major protocol violations - study 0102

Disease Subgroup Initial dose(mg/d)	Untreated			Treated		TOTAL	
	400 mg N=11	600 mg N=154	All N=165	400 mg N=26	600 mg N=69	All N=95	N=260
For both response analyses							
No documentation of Ph chromosome/Bcr-Abl positivity at baseline or on study	0	1(0.6)	1(0.6)	1(3.8)	2(2.9)	3(3.2)	4(1.5)
Not in the disease group as defined in the protocol	1 (9.1)	16(10.4)	17(10.3)	4(15.4)	10(14.5)	14(14.7)	31 (11.9)
accelerated phase	0	8(5.2)	8(4.8)	2(7.7)	6(8.7)	8(8.4)	16(6.2)
chronic phase	1 (9.1)	3(1.9)	4(2.4)	0	0	0	4(1.5)
chloroma	0	1 (0.6)	1 (0.6)	1 (3.8)	0	1 (0.1)	2(0.8)
unknown	0	4(2.6)	4(2.6)	1 (3.8)	4(5.8)	5(5.3)	9(3.5)
Forbidden antineoplastics during study	1 (9.1)	4(2.6)	5(3.0)	1 (3.8)	3(4.3)	4(4.2)	9(3.5)
For hematologic response only							
Less than two post-baseline efficacy assessments (in absence of PD/death)	1 (9.1)	18(11.7)	19(11.5)	3(11.5)	8(11.6)	11 (11.6)	30(11.5)
For cytogenetic response only							
No post-baseline efficacy assessments (in absence of PD/death)	0	15(9.7)	15(9.1)	2(7.7)	2(2.9)	4(4.2)	19(7.3)
No documentation of Ph+ at baseline	0	1 (0.6)	1 (0.6)	0	1 (1.4)	1 (1.4)	2(0.8)

6.5.3 Baseline demographic and background characteristics

The baseline demographic and disease subgroups and disease characteristics at baseline for the ITT population are summarized in tables 10 through 12.

Table 10 Baseline demographic characteristics-study 0102

Disease Subgroup	Untreated N=165	Treated N=95	TOTAL N=260
Age (yr) mean(SD)	56.5(13.0)	51.5(12.4)	54.7(13.0)
median	57	53	56
25-75th perc	50-66	43-61	47-64
min - max	19-81	20-73	19-81
Age category (n(%))			
< 50 yr	38(23.0)	37(38.9)	75(28.8)
>= 50 - < 60 yr	55(33.3)	31 (32.6)	86(33.1)
>= 60 - < 70 yr	44(26.7)	23(24.2)	67(25.8)
>= 70 yr	28(17.0)	4(4.2)	32(12.3)
Sex (n(%))			
male		85(52)	51 (54)136(52.3)
female		80(48)	44(46)124(47.7)
Race (n(%))			
Caucasian		138(84)	83(87) 221 (85.0)
Black	15(9)	6(6)	21(8.1)
Oriental	4(2)	1 (1)	5(1.9)
Other	8(5)	5(5)	13(5.0)

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Table 11 Disease subgroups at baseline -study 0102

Disease subgroup	Untreated N=165 (%)	Treated N=95 (%)	Total N=260 (%)
Time since first diagnosis of CML (n (%))			
< 6 months	18(10.9)	4(4.2)	22(8.5)
>= 6 months-<1 year	13(7.9)	6(7.4)	20(7.7)
>= 1 year <2 years	29(17.6)	19(20.0)	48(18.5)
>= 2 years <5 years	54(32.7)	32(33.7)	86(33.1)
>= 5 years	51 (30.9)	33(34.7)	84(32.3)
Time since first diagnosis of blast crisis (months)			
mean (SD)	1.1 (3.0)	7.2(19.8)	3.3(12.5)
median	0.4	2.8	0.6
25-75th percentiles	0-1	1-6 20-2 2	
min - max	0-36 ¹	0-148	0-148 ²
Prior antineoplastic therapy for accelerated phase/blast crisis			
Anthracyclines ³		53(56)	
Etoposide		23(24)	
Cytarabine		63(66)	
Topotecan		8(8)	
Corticosteroids ⁴		7(7)	
Nitrogen mustards ⁵		13(14)	
Methotrexate		8(8)	
Purine analogues ⁶		10(11)	
Others ⁷		29(31)	

1. patient 012 0001 was marked as having been in blast crisis, without antineoplastic treatment, or any notion of treatment, for 36 months. The next highest duration of blast crisis in this subgroup was 5 months

2. Extreme durations since blast crisis diagnosis (more than ten years) were recorded in patients 001 0001 (148 mos, after BMT), and 001 0003 (124 months, a return to chronic phase after antineoplastic drug therapy being followed by 7 years interferon treatment)

3 = daunorubicin, idarubicin, mitoxantrone; 4 = prednisone, prednisolone, dexamethasone; 5 = cyclophosphamide, ifosfamide, melphalan; 6 = mercaptopurine, thioguanine, fludarabine; 7 = vinblastine, vincristine, vindesine

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Table 12 Disease characteristics - study 0102

Disease subgroup	Untreated N=165	Treated N=95	Total N=260
Extramedullary involvement n (%)	118(71.5)	60(63.2)	178(68.5)
Splenomegaly			
> 0-<5cm	35(21.2)	19(20.0)	54(20.8)
>=5-<10cm	26(15.8)	8(8.4)	34(13.1)
>= 10 cm	43(26.1)	21 (22.1)	64(24.6)
Hepatomegaly			
> 0-<5cm	34(20.6)	20(21.1)	54(20.8)
>= 5 - <10 cm	11 (6.7)	6(6.3)	17(6.5)
>= 10 cm	3(1.8)	5(5.3)	8(3.1)
Lymph node	20(12.1)	4(4.2)	24(9.2)
Other	4(2.4)	3(3.2)	7(2.7)
WBC (109/L)			
mean (SD)	45(65.8)	55.9(60.8)	49(64.1)
median	26.9	38.5	29.5
25-75th percentiles	10.3-53.5	10.9-80.1	10.4-65.5
min - max	1.1-653.5	0.5-307.8	0.5-653.5
Platelets (109/L)			
mean (SD)	195(278)	133(168)	173(246)
median	88	63	75
25-75th percentiles	30-228	26-168	29-208
min - max	7-2160	6-963	6-2160
Blasts (%) in PB			
mean (SD)	34(28)	36(30)	35(29)
median	29	30	30
25-75th percentiles	10-51	11-60	10-56
min - max	0-100	0-96	0-100
Blasts (%) in BM			
mean (SD)	49(25)	52(23)	50(24)
median	45	54	46
25-75th percentiles	32-70	34-70	3 2-70
min - max	3-99		
ECOG performance status n(%)			
missing	7(4)	3(3)	10(3.8)
grade 0	34(21)	8(8)	42(16.2)
grade 1	67(41)	41 (43)	108(41.5)
grade 2	55(33)	42(44)	97(37.3)
grade 3	2(1)	1 (1)	3(1.2)

6.5.4 Dosage

Prior to amendment 2, patients began at a dosage of 400 mg/d. After amendment 2 the initial dosage became 600mg/d for newly recruited patients. Up-titration to 600mg (for the 400mg/d patients) and to 800mg (given bid) was permitted for improved efficacy in all patients. Dosage information is provided in Table 13 for the ITT population.

Table 13 Patients with drug dosage changes- study 0102

Initial dose (mg/d)	400mg/d N=37	600mg/d N=223	All doses N=260
No. of patients without change of initial dose	9(24.3)	84(37.7)	93(35.8)
No. of patients with change of initial dose	28(75.7)	139(62.3)	167(64.2)
Change of initial dose:			
Reduction at any time	19(51.4)	104(46.6)	123(47.3)
Escalation at any time	18(48.6)	64(28.7)	82(31.5)
Interruption at any time	9(24.3)	56(25.1)	65(25.0)

6.5.5 Patient exposure

Table 14 summarizes the numbers of patients by cumulative (3-monthly) durations of exposure.

Table 14 Dose intensity and exposure-study 0102

Initial dose(mg/d)	400 mg N=37	600 mg N=223	All doses N=260
Duration of exposure (days)			
mean (SD)	147(124)	108(64)	114(76)
median	114	99	99
25-75th percentiles	47-180	57-159	56-166
min - max	14-420	3-258	3-420
Duration of exposure n (%)			
<3 months	16(43.2)	100(44.8)	116(44.6)
3 months	12(32.4)	88(39.5)	100(38.5)
6 months	6(16.2)	35(15.7)	41 (15.8)
12 months	3(8.1)	0	3(1.2)
Actual dose intensity (mg/d)			
Mean (SD)	402(80)	556(99)	534 (110)
median	400	600	600
25-75th percentiles	363-453	500-600	453-600
min - max	225-560	225-775	225-775

6.5.6 Primary efficacy results

The primary efficacy variable in this study is confirmed hematologic response, as defined earlier into complete hematologic remission (CHR), no evidence of leukemia (NEL) and return to chronic phase (RTC).

Based on the recorded data the response rate was 26.2% for untreated and treated patients combined (Table 15). In the primary target population of previously untreated patients, the response rate was 30.3% (compared to 18.9% in the previously treated patients). With the 95% CI being between 23.4 and 37.9%, the success criteria for this study were achieved. With a response rate of 30.3% in this group, the target response rate was also achieved.

By dosage subgroup, the response rate was greater in the 600mg/d group than in the 400mg/d group (28.7% v 10.8%). This difference in the two dosage groups was apparent in both the untreated patients (32% v 9%) and the treated (22% v 12%).

As noted earlier, one center failed a GCP audit (center 7), and the primary efficacy analysis was repeated without the 7 patients from this center. This had no impact on the hematologic response rates presented here for the ITT population.

Table 15 Hematologic response-study 0102

Disease subgroup	Untreated N=165	Treated N=95	TOTAL N=260
Hematologic response:			
overall	50(30.3)	18(18.9)	68(26.2)
95% CI	23.4-37.9	11.6-28.3	20.9-31.9
Complete hem. remission	7(4.2)	3(3.2)	10(3.8)
No evidence of leukemia	7(4.2)	1 (1.1)	8(3.1)
Return to chronic phase	36(21.8)	14(14.7)	50(19.2)
Absence of Response	96(58.1)	66(69.5)	162(62.3)
No response ¹	50(30.3)	34(35.8)	84(32.2)
Progression without response	37(22.4)	29(30.5)	66(25.4)
Death without response	9(5.5)	3(3.2)	12(4.6)
Not-assessable²	19(11.5)	11(11.6)	30(11.5)

1. values available to indicate absence of response

2. not done; or values available not allowing determination of presence or absence of response and its confirmation

The time to response and preliminary duration of hematologic response analysis is summarized in Table 16.

Table 16 Time to, and duration of hematologic response-study 0102

Disease subgroup	Untreated N=165	Treated N=95	TOTAL N=260
Number of responders	50	18	68
Time to response			
Median	1.0	1.0	1.0
25-75th perc.	1.0-1.2	1.0-1.0	1.0-1.1
Range	0.9-2.1	0.9-2.0	0.9-2.1
Duration of response			
No censored values	39	10	49
Median	NA	6.6	6.6
25-75th perc.	5.4-NA	4.6-NA	4.7-NA

9.2.2. Overall hematologic response according to baseline characteristics

The confirmed hematologic response when analyzed by demographic variables (Table 17) suggests that there is no relevant difference in response rate between men and women but that the response rate may, surprisingly, improve with increasing age.

Table 17 Overall hematologic response by baseline characteristics-study 0102

Demographic characteristic		Untreated N=165	Treated N=95	TOTAL N=260
All patients	(n)	165	95	260
	Responders	50(30.3)	18(18.9)	68(26.2)
	95% CI	23.4-37.9	11.6-28.3	20.9-31.9
Sex: Male	n	85	51	136
	Responders	23(27.1)	9(17.6)	32(23.5)
	95% CI	18.0-37.8	8.4-30.9	16.7-31.6
Female	n	80	44	124
	Responders	27(33.8)	9(20.5)	36(29.0)
	95% CI	23.6-45.2	9.8-35.3	21.2-37.9
Age <50	n	38	37	75
	Responders	8(21.1)	5(13.5)	13(17.3)
	95% CI	9.6-37.3	4.5-28.8	9.6-27.8
50-60	n	55	31	86
	Responders	12(21.8)	5(16.1)	17(19.8)
	95% CI	11.8-35.0	5.5-33.7	12.0-29.8
60-70	n	44	23	67
	Responders	18(40.9)	6(26.1)	24(35.8)
	95% CI	26.3-56.8	10.2-48.4	24.5-48.5
70	n	28	4	32
	Responders	12(42.9)	2(50.0)	14(43.8)
	95% CI	24.5-62.8	6.8-93.2	26.4-62.3

Cytogenetic response

The analysis of cytogenetic response is of *unconfirmed* response because of the interval between bone marrow aspirations and cytogenetic evaluations (monthly for the first 3 months, three monthly thereafter).

The overall response is given in table 18 for the ITT population.

The time to response and duration of response are summarized in table 19.

Table 18 Cytogenetic response (unconfirmed)-study 0102

Disease subgroup	Untreated N=1165	Treated N=95	TOTAL N=260
Major response (CCyR+ PCyR)	20(12.1)	15(15.8)	35(13.5)
95% CI	7.6-18.1	9.1-24.7	9.6-18.2
Complete	8(4.8)	5(5.3)	13(5.0)
Partial	12(7.3)	10(10.5)	22(8.5)
Minor	4(2.4)	2(2.1)	6(2.3)
Minimal	18(10.9)	9(9.5)	27(10.4)
Absence of Response			
No response	70(42.4)	29(30.5)	99(38.1)
Progression without response	30(18.2)	28(29.5)	58(22.3)
Death without response	6(3.6)	5(5.3)	11 (4.2)
Not assessable			
Ph negative at baseline	2(1.2)	3(3.2)	5(1.9)
Not done	15(9.1)	4(4.2)	19(7.3)

Table 19 Duration and time to major cytogenetic response-study 0102

Disease subgroup	Untreated N=1165	Treated N=95	TOTAL N=260
Number of responders	20	15	35
Time to response			
Median	2.3	2.6	2.6
25-75th perc.	1.5-2.8	1.0-3.0	1.0-2.8
Range			
Duration of response			
No censored values	12	5	17
Median	2.8	1.6	2.5
25-75th perc.	1.1-4.8	1.0-3.2	1.1-4.8

9.2.4. Cancer related symptoms and ECOG performance status

Symptoms known to be associated with CML (fever, night sweats, bone pain, arthralgia, abdominal discomfort) were scored according to CTC grading and assessed every 3 months and at the time of discontinuation. The majority of patients were without symptoms except at the time of discontinuation. These results are indicated in Table 20.

Table 20 Cancer related symptoms-study 0102

Symptom	Grade	Baseline (N=260)	3 Months (N=260)	6 Months (N=170)
Abdominal discomfort	Absent	201 (77.3%)	135(51.9%)	67 (39.4-1.)
	Grade 1	35 (13.5%)	8 (3.1%)	3 (1.8%)
	Grade 2	14 (5.4%)	1 (0.4%)	1 (0.6%)
	Grade 3	10 (3.8%)	0	0
	Grade 4	0	0	0
	Progression	0	77 (29.6%)	78 (45.9%)
	Death	0	13 (5.0%)	12 (7.1%)
	Missing	0	26 (10.0%)	9 (5.3%)
Bone pain	Absent	205 (78.8%)	133 (51.2%)	63 (37.1%)
	Grade 1	20 (7.7%)	5(1.9%)	4 (2.4%)
	Grade 2	22 (8.5%)	5 (1.9%)	2 (1.2%)
	Grade 3	9 (3.5%)	0	2 (1.2%)
	Grade 4	4 (1.51s)	1 (0.4%)	0
	Progression	0	77 (29.6%)	78 (45.9%)
	Death	0	13 (5.0%)	12 (7.1%)
	Missing	0	26 (10.0%)	9 (5.3%)
Arthralgia	Absent	218 (83.8%)	132 (50.8%)	64 (37.6%)
	Grade 1	19 (7.3%)	6 (2.3%)	4 (2.4%)
	Grade 2	17 (6.5%)	5 (1.9%)	1 (0.6%)
	Grade 3	6 (2.3%)	0	2 (1.2%)
	Grade 4	0	1 (0.4%)	0
	Progression	0	77 (29.6%)	78 (45.9%)
	Death	0	13 (5.0%)	12 (7.1%)
	Missing	0	26 (10.0%)	9 (5.3%)
Fever	Absent	184 (70.8%)	139 (53.5%)	64 (37.6%)
	Grade 1	45 (17.3%)	4 (1.5%)	4 (2.4%)
	Grade 2	24 (9.2%)	0	1 (0.6%)
	Grade 3	6 (2.3%)	1 (0.4%)	2 (1.2%)
	Grade 4	1 (0.4%)	0	0
	Progression	0	77 (29.6%)	78 (45.956)
	Death	0	13 (5.0%)	12 (7.116)
	Missing	0	26 (10.0%)	9 (5.3%)
Night Sweats	Absent	173 (66.5%)	133 (51.2%)	69 (40.6%)
	Grade 1	47 (18.1%)	7 (2.7%)	1 (0.6%)
	Grade 2	32 (12.3%)	2 (0.6%)	0
	Grade 3	5 (1.9%)	2 (0.8%)	1 (0.6%)
	Grade 4	3 (1.2%)	0	0
	Progression	0	77 (29.6%)	78 (45.9%)
	Death	0	13 (5.0%)	12 (7.1%)
	missing	0	26 (10.0%)	9 (5.3%)

The ECOG performance rating was also assessed at baseline and at each month as well as at the time of discontinuation, These results are recorded in Table 21.

Table 21 Performance status - study 0102

Treatment group	ECOG Performance	Baseline	3 Months	6 Months
	score	(N=260)	(N=260)	(N=170)
400 mg	Grade 0	7 (18.9%)	1 (2.7%)	2 (5.4%)
	Grade 1	15 (40.5%)	11 (29.7%)	8 (21.6%)
	Grade 2	15 (40.5%)	5 (13.5%)	1 (2.7%)
	Grade 3	0	0	1 (2.7%)
	Grade 4	0	0	0
	Progression	0	11 (29.7%)	19 (51.4%)
	Death	0	3 (8.1%)	3 (8.1%)
	Missing	0	6 (16.2%)	3 (8.1%)
	Total	37 (100%)	37 (100%)	37 (100%)
	600 mg	Grade 0	35 (15.7%)	54 (24.2%)
Grade 1		93 (41.7%)	56 (25.1%)	19 (14.3%)
Grade 2		82 (36.8%)	9 (4.0%)	8 (6.0%)
Grade 3		3 (1.3%)	1 (0.4%)	1 (0.8%)
Grade 4		0	0	0
Progression		0	66 (29.6%)	59 (44.4%)
Death		0	10 (4.5%)	9 (6.8%)
Missing		10 (4.5%)	27 (12.1%)	8 (6.0%)
Total		223 (100%)	223 (100%)	133 (100%)
All doses		Grade 0	42 (16.2%)	55 (21.2%)
	Grade 1	108 (41.5%)	67 (21.2%)	27 (15.9%)
	Grade 2	97 (37.3%)	14 (5.4%)	9 (5.3%)
	Grade 3	3 (1.2%)	1 (0.4%)	2 (1.2%)
	Grade 4	0	0	0
	Progression	0	77 (29.6%)	78 (45.9%)
	Death	0	13 (5.0%)	12 (7.1%)
	Missing	10 (3.8%)	33 (12.7%)	11 (6.5%)
	Total	260 (100%)	260 (100%)	170 (100%)

Frequency analysis of the ECOG grades, comparing unconfirmed hematologic responders with non-hematologic responders at the 3 and 6 month timepoints shows that overall the responders had better scores than the non-responders. The differences were marginal but consistent at both timepoints.

9.2.5. Overall survival

Table 22 indicates the overall survival in months of patients on this study. By Kaplan-Meier analysis, the current estimated probabilities of survival are

- at 6 months:
 - 60.3% (95%CI: 51.5-69.0%) in the untreated group
 - 43.1% (95%CI: 32.4-53.9%) in the treated group
- at 9 months.
 - 32.8% (95%CI: 12.9-52.8%) in the untreated group
 - 34.5% (95%CI: 22.8 - 46.2%) in the treated group

Table 22 Survival-study 0102

Disease subgroup	Untreated N=165	Treated N=95	TOTAL N=260
Overall survival (months)			
No. censored	101	41	142
median	7.1	5.2	6.3
95% CI	6.1-9.6	4.0-7.2	5.6-8.6

6.6 FDA Results Study 0102

6.6.1 Patient Characteristics

Demographic and clinical characteristics of blast crisis patients participating in study 0102 are indicated in Table 23. As is evident in this table patients enrolled in this study may or may not have had prior therapy for accelerated phase/blast crisis disease and they may have been treated with either STI-571 400 mg or 600 mg/day. The majority of study patients were performance status 0 or 1. As expected the majority of study patients had extramedullary disease and had chromosomal abnormalities in addition to the Philadelphia chromosome.

Table 23 Patient demographics per FDA-study 0102

Characteristic	Value (N=260)
Age	
Median (range)	56 (19-81)
Sex	
Male	136 (52%)
Female	124 (48%)
Race	
Caucasian	221 (85%)
Black	21 (8%)
Other	18 (7%)
Performance status (ECOG)	
0	42 (16%)
1	108 (42%)
2	97 (37%)
3	3 (1%)
Unknown	10 (4%)
Prior therapy (blast crisis/accel phase)	
Yes	95 (37%)
No	165 (63%)
Chromosomal abnormalities	
Ph positive only	94 (36%)
Ph pos + Other chromosome abnormalities	166 (64%)
Extramedullary disease	
Yes	178 (68%)
No	82 (32%)
STI-571 Starting Dose	
400 qd	37 (14%)
600 qd	223 (86%)

6.6.2 Hematologic Response

The primary efficacy endpoint is confirmed hematologic response. As indicated in Table 24 hematologic response was further characterized as either complete, no evidence of leukemia or return to chronic phase disease. While there are 4 separate groups of patients based on the variables of prior therapy and STI-571 dose the results are not presented separately for each category because of small numbers and presumably wide confidence intervals for each result.

Hematologic response data in the FDA analysis was comparable to the sponsor's confirmed hematologic response analysis. In both analyses 68 (26%) of patients had a confirmed hematologic response. The median duration of response differs somewhat in the FDA and sponsor analyses, 5.6 months in the former and 6.6 months in the latter. The likely reason for this difference, based on sponsor review of FDA results, is differing censoring schema. In the FDA analysis responders who were not evaluated at a protocol specified time and who progressed on a delayed evaluation were censored on the date of their last protocol specified evaluation for hematologic response whereas the sponsor declared progression on the delayed date.

Table 24 Hematologic response per FDA-study 0102

Characteristic	N=260
Total Hematologic Responders	68 (26%)
Best hematologic response	
Complete	11 (16%)
No evidence of leukemia	7 (10%)
Return to chronic phase	50 (74%)
Time to hematologic response- median (d)	29 (26-64)
Censored for response duration	57 (84%)
Response duration- median (m)	5.6

6.6.3 Cytogenetic Response

Major cytogenetic response was a secondary efficacy endpoint. Fourteen patients were found to have a major cytogenetic response at the time of their baseline disease evaluation. This group presumably included the 4 patients who were Philadelphia chromosome negative at baseline and probably also included 10 individuals who had responded to blast crisis or accelerated disease therapy prior to enrollment into this study. Follow-up results of these patients is indicated in Table 25. As indicated, 3 patients maintained their cytogenetic response after starting on STI-571 and a fourth lost and then regained a cytogenetic response.

Table 25 Baseline cytogenetic response-study 0102

Number of McyR's at baseline	N=14
Follow-up	
• No subsequent cytogenetic studies	7
• Lost CyR by at next study	3
• Maintained McyR on at least 1 F/U exam	3
• Lost and then regained McyR	1

Results of cytogenetic response analysis is summarized in Table 26. In FDA discussions with the sponsor it was the FDA's position that cytogenetic responses should be confirmed by a second evaluation at least one month after the initial response determination and that an adequate specimen would have at least 20 evaluable metaphases. Because of these stipulations and because the sponsor counted individuals with both confirmed and unconfirmed responses as major cytogenetic responses (MCyR's). Table 26 indicates results for all relevant subgroups. Similar to the sponsor's analysis the FDA found that 35 of 260 patients (14%) had at least one marrow cytogenetic evaluation that demonstrated a MCyR. The FDA censored a total of 22 cytogenetic responders for response duration while the sponsor censored 17. Among patients who had a major CyR on at least 2 cytogenetic evaluations the FDA censored 10/11 (91%) of patients who had 20 or more metaphases counted on the two evaluations and 13 of 14 (93%) of patients who had less than 20 metaphases evaluated on at least one evaluation. The median duration of cytogenetic response was not determinable in the FDA analysis and 2.5 months in the sponsor's analysis.

Table 26 Cytogenetic response during treatment per FDA-study 0102

	>=20 metaphases (N=35)		Irrespective of # of metaphases (N=35)	
	Confirmed*	Unconfirmed	Confirmed	Unconfirmed
Major CyR	11	24	14	21
Complete	3	6	6	3
Partial	8	18	8	18
Censored for response duration	10/11 (91%)		13/14 (93%)	
Median Response Duration [d] (range)	Not determinable at this time		Not determinable at this time	

Confirmed - At least 2 marrows confirm a major cytogenetic response

Unconfirmed - Only a single marrow indicates a major cytogenetic response

In view of the prognostic importance attributed to a MCyR it was of interest to observe that patients may enter into, leave and return to major cytogenetic response status.

Table 27 documents the course of three such patients. Patient 4-3 after attaining a partial response (35% Ph+cells), lost that response on day 88 (>65-95% Ph+cells) and then regained it on day 166. Patient 509-9 went into and out of major cytogenetic response on two occasions while patient 506-4 had partial cytogenetic responses separated by examinations revealing minimal and no cytogenetic response.

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Table 27 Variable cytogenetic response during therapy per FDA-study 0102

Patient	Study day	CyR
4-3	60	Partial
	88	Minimal
	166	Partial
	249	Partial
509-9	28	Partial
	54	Minor
	91	Partial
	168	Minor
506-4	0	Partial
	35	Minimal
	63	None
	91	Partial
	144	Minimal

6.6.4 Hematologic plus cytogenetic response

Because of the prognostic importance of both hematologic and cytogenetic response it is of interest to determine whether they track together in patients. As indicated in Table 28 fifty-six patients had a hematologic response and 35 had a major cytogenetic response. Of interest only 20 patients had both.

Table 28 Hematologic and cytogenetic responses per FDA-study 0102

Efficacy response	No. of Pts
HR	68
MCyR	35
CHR + MCyR	20
CHR without MCyR	48
MCyR without CHR	15

6.6.5 Symptom relief

An important aspect of treatment is symptom relief. Table 29 describes common symptoms of CML patients and indicates their severity on three sequential evaluations. There appears to be a reduction in grade 1, 2 and 3 symptoms with STI-571 treatment on the day 85 evaluation and a return of symptoms by the day 169 evaluation

Table 29 Symptom relief per FDA-study 0102

Visit	Symptom (No of pts)	Grade					ND
		0	1	2	3	4	
-1 d -7 to 0	Abdominal Discomfort (261)	201	36	14	10	0	0
	Arthralgia (260)	218	19	17	6	0	0
	Bone Pain (260)	205	20	22	9	0	4
	Fatigue (55)	0	31	17	6	0	1
	Fever (260)	184	45	24	6	0	1
	Night Sweats (260)	173	47	32	5	3	0
22 d 85	Abdominal Discomfort (155)	136	8	1	0	0	10
	Arthralgia (154)	132	5	5	0	0	12
	Bone Pain (154)	133	5	5	0	0	111
	Fatigue (27)	12	10	5	0	0	0
	Fever (154)	139	4	0	1	0	10
	Night Sweats (154)	133	7	2	2	0	10
28 d 169	Abdominal Discomfort (216)	140	16	6	4	0	48
	Arthralgia (216)	144	14	7	2	0	48
	Bone Pain (216)	135	13	12	6	0	48
	Fatigue (35)	12	7	11	3	0	2
	Fever (216)	117	28	13	8	0	49
	Night Sweats (216)	145	11	10	3	0	47

ND = No data

6.6.6 Performance status changes

Performance status evaluation is shown in Table 30. For pretreatment performance status 1 or 2 patients a total of 65 individuals improved their performance status (at least 2 consecutive evaluations separated by at least 1 month) during treatment.

Table 30 Performance status changes per FDA-study 0102

Initial P.S.	No. of Pts	Change in Performance Status			
		Improved	Stable	Worse	No data
0	42	--	17	25	0
1	108	34	48	22	4
2	97	31	28	35	3
3	3	0	1	1	1

7.0 Study 0109

A phase II study to determine the safety and anti-leukemic effects of STI571 in adult patients with Philadelphia chromosome positive leukemia including acute lymphoblastic leukemia, acute myeloid leukemia, lymphoid blast crisis chronic myeloid leukemia and accelerated phase chronic myeloid leukemia. First patient recruited 09-Aug-99, last patient recruited 12-May-00

7.1 Patient population

The target population included male and female, adult patients with Ph+ CML in accelerated phase (100 planned), or relapsed/refractory Ph+ ALL (30 planned) or Ph+ AML (15 planned). Therefore, the total sample size was planned to be 145 patients (protocol amendment 2), based on Fleming's one stage design for the primary disease group, Ph+ CML in accelerated phase, and practical considerations for the two exploratory disease groups, Ph+ ALL or Ph+ AML.

The original protocol also planned to include 29 patients with Ph+ CML in lymphoid blast crisis as a third exploratory disease group, but recruitment of these patients was put on hold after protocol amendment I (dated 05 Oct 99) and not reactivated after protocol amendment 2 (dated 21 Dec 99), due to the less durable response to single agent therapy with STI571 in this disease group in the phase I study 001.

7.2 Inclusion and exclusion criteria

Patients who were included were those:

Male or female, aged 18 years, with a histologically confirmed diagnosis of Ph+ leukemia of one of the following types:

- accelerated phase CML, never in blast crisis before starting treatment, with one or more of the following criteria present within 4 weeks prior to administration of the first dose of treatment (these conditions defined in protocol amendment 2, 21-Dec 99):
 - 15% but <30% blasts in blood or bone marrow
 - 30% blasts plus promyelocytes in peripheral blood or bone marrow (providing that <30% blasts present in bone marrow)
 - peripheral basophils 20%
 - thrombocytopenia <100 x 10⁹ /L unrelated to therapy.
- ALL or AML in first or subsequent relapse after either standard chemotherapy, autologous or allogeneic bone marrow transplantation, or high-dose treatment with peripheral blood stem cell support, or
- ALL or AML refractory to standard chemotherapy (no complete remission achieved after two courses of conventional induction chemotherapy).
- Blastic phase of CML in first or subsequent relapse or refractory to standard chemotherapy (as for AML or ALL) up to the date of protocol amendment 1, 05-Oct 99, when recruitment was put on hold. After protocol amendment 2 (21 -Dec-99), recruitment of this disease group was stopped.

- With serum AST (SGOT) and ALT (SGPT) not more than 3 x upper limit of normal (ULN) (or not more than 5xULN if clinically suspected leukemic involvement of the liver), serum creatinine concentration not more than 2xULN, and total serum bilirubin level not more than 3xULN (bilirubin limit was 1.5xULN before protocol amendment 1)
- Who, if female and of childbearing potential, had a negative pregnancy test prior to the initiation of study drug, and, for both sexes, used barrier methods of contraception throughout the study
- Who had given voluntary written informed consent.

Patients who were excluded were those:

- Who had an ECOG performance status score ≥ 3 with known leukemic involvement of the CNS
- interferon- α within 48 hours, hydroxyurea within 24 hours, homoharringtonine within 14 days, low-dose, moderate dose or high dose cytosine arabinoside within 7, 14 or 28 days respectively, 6-mercaptopurine, vinca alkaloids or steroids within 7 days, anthracyclines, mitoxantrone, etoposide, methotrexate, cyclophosphamide within 21 days, or busulfan within 6 weeks.
- who had undergone hematopoietic stem cell transplantation within six weeks of Day 1, or who had not achieved full hematopoietic recovery following the transplant. with grade 3/4 cardiac disease or any serious, concomitant, medical condition
- with a history of non-compliance to medical regimens or who were considered potentially unreliable.

7.3 Protocol amendments

Three amendments were made to the protocol. These have been incorporated into the descriptions within the methodology sections, and the significant changes from the original protocol are summarized below:

Amendment 1 (05 October 1999)

The main changes are summarized as follows:

- Recruitment to the three exploratory disease groups: Ph+ CML in LBC, Ph+ ALL, Ph+ AML, was put on hold.
- Patients with total serum bilirubin not more than 3 x ULN were allowed to enter the study.
- It was decided to limit the number of patients treated at 400mg/day in this study, and to add a cohort at 600mg/day.
- Dose escalation from 400 to 600mg/day for patients who became resistant or relapsed while receiving ST1571 treatment was allowed.
- Trough plasma concentrations of ST1571 on days 8 and 28 were to be determined in patients from US centers only.
- Patients were allowed to be followed at the referral center after a minimum period of two months of follow-up at the study center.
- Fluorescence in situ hybridization (FISH) analysis was to be performed on bone marrow samples with less than 20 identified metaphases for cytogenetics.

Amendment 2 (21 December 1999)

The main changes are summarized as follows:

Additional patients with accelerated phase CML were to be recruited onto the study at the 600mg/day-dose level, after significant initial response rates in this population.

Patients with CML in accelerated phase were to be included only if they had never been in the blastic phase of the disease.

The adult Ph+ ALL and AML groups were to be re-opened for accrual, after analysis of data from the Phase I study showed significant response rates in these groups.

Accrual into the CML LBC disease group was discontinued.

Patients receiving therapy with drugs known to significantly affect gastric pH were allowed to enter the study.

Patients with disease progression while on STI571 treatment at a dose of 600mg/day could have their dose increased to 800mg, administered as 400mg twice daily, after no serious drug-related adverse events were recorded in the cohort of patients receiving a similar dose in the Phase I study.

The dose reduction steps for non-hematological toxicity were simplified.

Procedures for management of grade 4 neutropenia were modified.

The evaluation of PK of STI571 was extended, by implementing a population PK study that included patients in CML in accelerated phase only.

The statistical section of the protocol was revised.

Amendment 3 (30 August 2000)

The main changes are summarized as follows:

Patients were allowed to take STI571 immediately before and during meals, following results from a study, which showed that the effect of food on the bioavailability of STI571 was minimal.

During Part 2 of the study only, the monthly requirement for patient's evaluation at the study center was changed to 3-monthly during the first 6 months and 4-monthly thereafter. The monthly visits could be conducted at the referral site.

The supply of STI571 to patients was changed to monthly during study Part 1, 3-monthly during the first 6 months of Part 2 and 4-monthly thereafter.

7.4 Other changes in study conduct

A central independent laboratory was planned to be used for review of bone marrow and peripheral blood histopathology slides to confirm the diagnosis of CML in lymphoid blast crisis. Since recruitment of patients in this disease group was put on hold after amendment 1 and stopped completely after amendment 2, the central review procedure was no longer necessary and was not performed on any patient samples.

An internal GCP audit on ~~the~~ revealed some unauthorized procedures contrary to GCP. For his own research purposes, the investigator performed an unapproved/unauthorized PK study on 4 patients from whom blood samples were taken to measure STI571 plasma concentrations in the presence or absence of the antibiotic, Dalacin (clindamycin) administered

iv at high doses. Novartis instructed the investigator to stop these unapproved studies and reminded him of his commitments to follow GCP, obtain Ethics Committee approval and patient informed consent.

It was decided to analyze the primary efficacy data with and without the data from the 14 patients enrolled in ~~the~~ in case the additional procedures carried out may have affected the efficacy results.

7.5 Statistical methods

Data were analyzed by Novartis personnel. The main focus is on the results in the primary disease group: CML in accelerated phase, the other three acute leukemia disease groups are exploratory only.

Populations

Intent-to-treat (ITT) population consists of all enrolled patients.

Safety population consists of all patients who received at least one dose of study medication. As all patients enrolled were also treated the ITT and Safety populations are identical.

Per protocol (PP) population is a subset of the ITT population without major violations of the protocol (i.e. violations likely to significantly compromise the design of the study as regards the assessment of the drug's efficacy in patients at this phase of the disease).

Major protocol violations taken as disqualifying patients from the per protocol populations were as follows:

for hematologic and cytogenetic response assessments

- patient not in the defined phase of CML as defined in the protocol
- documented Ph chromosome negativity
- administration of proscribed antineoplastic drugs during treatment with STI571 (hydroxyurea for more than one week or Ara-C, interferon, busulfan, etoposide, anthracyclines, mitoxantrone).

for hematologic response assessment only

- absence of two post-baseline efficacy assessments at least 4 weeks apart in patients not dying or discontinuing treatment because of treatment failure (adverse event or abnormal laboratory value, unsatisfactory therapeutic effect)

for cytogenetic response assessment only

- absence of at least one post-baseline bone marrow cytogenetic assessment in patients not dying or discontinuing treatment because of treatment failure (adverse event or abnormal laboratory value, unsatisfactory therapeutic effect)

All other protocol violations were qualified as minor because they were unlikely to compromise the efficacy assessment in a significant manner. Examples of such minor violations were:

- absence of evidence for Ph chromosome positivity (by karyotype) at baseline if there was evidence for Bcr-Abl positivity by FISH or positivity thereafter during study
- abnormal liver or renal function
- ECOG performance status score ≥ 3
- insufficient wash-out period for prior antineoplastics

Deviations from the protocol

The protocol's definitions of populations were different from those given above. The changes were made following recommendations from the FDA. The protocol specified the primary efficacy analysis to be based on ITT, which was defined as all patients who received at least one dose of medication and had at least one post-baseline efficacy assessment. The PP population was defined as those patients who received one dose of medication and participated in the study without major deviations from the protocol procedures.

Primary efficacy variable

The primary efficacy variable in this study was the **confirmed overall hematologic response** which was the best of the individual response assessments and was categorized as either complete hematologic remission, no evidence of leukemia or return to chronic phase. For definitions of primary and secondary efficacy variables see section 5.2.5 of this report.

Deviations from the protocol

According to the protocol, loss of hematologic response was defined as relapse or progression, where relapse was considered as blasts $\geq 30\%$ in peripheral blood or bone marrow. This was not considered strict enough and a more conservative approach was adopted whereby an assessment with $\geq 15\%$ blasts or any other value no longer qualifying for RTC would be considered as indicating loss of response. In addition, the presence of EMD other than liver and spleen enlargement was also taken to indicate **blast crisis** and consequently loss of response.

Time to blast crisis

This duration was calculated for all patients as the time between start of treatment and the earliest date of the following:

- progression to blast crisis ($\geq 30\%$ blasts in PB or BM, extramedullary disease other than liver/spleen enlargement)
- discontinuation due to AE, lab abnormality, unsatisfactory therapeutic effect or death

For patients who never responded, progression to blast crisis was taken to be the date of their first post-baseline assessment consistent with blast crisis.

For patients who were in blast crisis at study entry and responded during therapy, progression to blast crisis was evaluated only after they had responded.

Time to progression

This duration was calculated for all patients as the time between start of treatment and the earliest of the following:

- loss of response (when any of the criteria for hematologic response were no longer fulfilled)
- progression to blast crisis ($\geq 30\%$ blasts in PB or BM, extramedullary disease other than liver/spleen enlargement)
- discontinuation due to AE, lab abnormality, unsatisfactory therapeutic effect or death.

Secondary efficacy variable

Major cytogenetic response (MCyR) defined as "complete (CCyR)" or "partial (PCyR)".

As the follow-up time in this study was short (and it generally is in this patient population) most patients had only one or two available bone marrow cytogenetic assessments. Consequently, the analyses are principally of **unconfirmed** cytogenetic responses. Nevertheless, the rate of confirmed cytogenetic responses was calculated in addition.

Times to event analyses for cytogenetic response were calculated, as additional analyses (not specified in the protocol), as detailed below.

Time to major cytogenetic response

This was defined for all patients with major cytogenetic response as the time until first documented complete or partial cytogenetic response.

Duration of major cytogenetic response

This duration was evaluated for all patients with major cytogenetic response and was defined as the time between first documented complete or partial response and the earliest of the following

- loss of response (increase by $\geq 30\%$ Ph+ cells compared to lowest value before current assessment or an increase to $\geq 65\%$ Ph+ cells). For CCyR an increase to $>0\%$ Ph+ cells was considered a loss of complete cytogenetic response).
- discontinuation due to AE, lab abnormality, unsatisfactory therapeutic effect or death.

Patients still on the study at the date of cut-off were censored at the time of their last bone marrow evaluation for cytogenetics, as long as there was no evidence of loss of major cytogenetic response. Patients discontinuing were censored at the time of the last bone marrow evaluation if the discontinuation was for reasons other than AE, lab abnormality, unsatisfactory therapeutic effect or death.

Overall survival

The overall survival was calculated for all patients as the time between start of treatment and death. Censoring was carried out as follows:

at time of discontinuation for patients discontinuing to undergo bone marrow transplant at the last examination date for patients still on study at the date of cut-off at the date of last contact for patients discontinued and followed up for survival.

Other Secondary endpoints

ECOG performance status and cancer related symptoms.

Sample size and power considerations

The sample size was based on Fleming's single stage, single arm procedure testing the (one-sided) hypotheses $H_0: p \leq p_0$ and $H_1: p \leq p_1$. This design is commonly used for Phase II studies. It specifies p_0 as the uninteresting response rate which usually is considered as the rate that does not warrant further investigation of the drug, and p_1 as the rate which should not be missed, i.e. which if true would imply that the treatment has therapeutic efficacy. In this study, $p_0=30\%$ and $p_1=50\%$.

The acceptable probabilities of making incorrect decisions were as follows: the probability of rejecting H_0 when in fact p is no more than 30% has to be less than 2.5% (one-sided) and the probability for rejecting H_1 when in fact p is no less than 50% has to be less than 10% (power=90%).

For the above consideration, and using binomial distribution, a minimal sample size of 68 patients was needed. The study "win criteria" were to be fulfilled when 29/68 responders were observed. To account for dropout rate, the sample size was increased to 100 patients with accelerated phase CML.

The patient population in this study exceeded the planned target of 100 patients in CML AP. There were 235 patients in this group as assigned by the investigators. The ALL disease group was also bigger than planned: 48 vs. 30.

7.6 Clinical data per sponsor

7.6.1 Patient disposition

A total of 293 patients entered the study with CML AP (235, 80%), ALL (48, 16%), AML 2 (1%) or LBC 8, (3%). Patient enrollment is indicated in Table 31.

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Table 31 Patient disposition-study 0109

Disease group: STI571 initial dose (mg/day):	CML AP (Primary group)			ALL	AML	LBC
	400 mg N=77	600 mg N=158	All doses N=235	All doses N=48	All doses N=2	All doses N=8
Number (%) of patients						
Enrolled	77(100)	158(100)	235(100)	48(100)	2(100)	8(100)
Total still on treatment	37(48.1)	117(74.1)	154(65.5)	5(10.4)	1(50.0)	2(25.0)
Total discontinued	40(51.9)	41 (25.9)	81 (34.5)	43(89.6)	1(50.0)	6(75.0)
Reason for discontinuation						
Adverse event(s)	2(2.6)	11 (7.0)	13(5.5)	2(4.2)	0	1(12.5)
Unsatisfactory therapeutic effect	31 (40.3)	26(16.5)	57(24.3)	34(70.8)	1(50.0)	4(50.0)
Patient to BMT	3(3.9)	1 (0.6)	4(1.7)	5(10.4)	0	0
Subject withdrew consent	0	2(1.3)	2(0.9)	0	0	0
Death §	4(5.2)	1 (0.6)	5(2.1)	2(4.2)	0	1 (12.5)

§ Includes only those patients for whom death was reported as the primary reason for discontinuation on the study phase completion/discontinuation CRF. From Table 31, only 8 patients appear to have died during the study. However a further 43 patients died within 28 days of the last dose of study drug.

7.6.2 Major Protocol deviations

Protocol violations were designated minor or major according to the way in which they were likely to affect the efficacy results. The major protocol violations are those that would affect the hematologic and/or cytogenetic efficacy analyses so that CML AP patients with these violations were excluded from the per protocol populations. These are reported in Table 32.

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Table 32 Major protocol violations-study 0109

Disease group: STI571 initial dose(mg/day):	CML AP (Primary group)		
	400 mg N=77	600 mg N=158	All doses N=235
Major PVs [n (%)]:			
For both per protocol response analyses:			
Not in the disease group as defined in the protocol	15(19.5)	39(24.7)	54(23.0)
chronic phase CML	4(5.2)	12(7.6)	16(6.8)
myeloid blast crisis	7(9.1)	22(13.9)	29(12.3)
disease group could not be calculated	4(5.2)	5(3.2)	9(3.8)
Forbidden antineoplastics during study	2(2.6)	1 (0.6)	3(1.3)
For per protocol hematological response only:			
Less than two post-baseline efficacy assessments for hematologic response (and no PD/death)	5(6.5)	17(10.8)	22(9.4)
For per protocol cytogenetic response only:			
No post-baseline efficacy assessments for cytogenetic response (and no PD/death)	6(7.8)	17(10.8)	23(9.8)
No documentation of Ph chromosome positivity at baseline	1 (1.3)	1 (0.6)	2 (0.9)

Abbreviations: PD = progressive disease

Rigorous, retrospective assessment of each patient in the CML AP disease group showed that the investigators' assignment to a disease group did not always follow the diagnostic criteria given in the protocol. Calculation of the disease group using these criteria led to some patients being re-assigned to another disease group, so that the calculated number of patients in the CML AP group was 181 (77%). For the remaining 54 (23%) of the 235 patients assigned to CML AP by the investigators: 29 were in blast crisis (BC), 16 in chronic phase CML and for 9 patients it was not possible to calculate their disease group. The 54 patients reassigned to BC, chronic CML or no disease group were excluded from the per protocol populations for hematologic and cytogenetic efficacy analyses.

Groupings for analysis

All patients who entered the study were included in the ITT and the safety populations. CML AP patients who were major protocol violators were excluded from one or both of the per protocol populations for efficacy analysis. The allocation of each patient to the respective populations is presented in Table 33.

Table 33 Number of CML AP patients-study 0109

STI571 initial dose (mg/day):	400 mg n(%)	600 mg n(%)	all doses n (%)
Population:			
ITT	77(100)	158(100)	235(100)
Safety	77(100)	158(100)	235(100)
Per Protocol, hematologic	57(74.0)	105(66.5)	162(68.9)
Per Protocol, cytogenetic	58(75.3)	107(67.7)	165(70.2)

7.6.3 Baseline demographic and background characteristics

The baseline demographics and disease characteristics of the ITT population are summarized in Tables 34 and 35.

Table 34 Baseline demographics-study 0109

STI571 initial dose	CML AP (primary group)			ALL N=48	AML N=2	LBC N=8
	400 mg N=77	600 mg N=158	all doses N=235			
Age (years)						
mean	53.4	57.0	55.8	47.1	42.5	57.4
SD	12.71	11.92	12.28	13.56	21.92	6.70
median	55.0	57.5	56.0	49.5	42.5	9.5
range						
Age groups n(%)						
<50 years	25(32.5)	37(23.4)	62(26.4)	24(50.0)	1 (50.0)	1 (12.5)
≥50 to <60 years	26(33.8)	54(34.2)	80(34.0)	15(31.3)	1 (50.0)	3(37.5)
≥60 to <70 yrs	21 (27.3)	43(27.2)	64(27.2)	7(14.6)	0	4(50.0)
≥70 years	5(6.5)	24(15.2)	29(12.3)	2(4.2)	0	0
Sex n(%)						
male	45(58.4)	73(46.2)	118(50.2)	24(50.0)	1(50.0)	4(50.0)
female	32(41.6)	85(53.8)	117(49.8)	24(50.0)	1(50.0)	4(50.0)
Race n(%)						
caucasian	69(89.6)	141 (89.2)	210(89.4)	40(83.3)	2(100)	7(87.5)
black	3(3.9)	7(4.4)	10(4.3)	3(6.3)	0	1(12.5)
oriental	1 (1.3)	1 (0.6)	2(0.9)	3(6.3)	0	0
other	4(5.2)	9(5.7)	13(5.5)	2(4.2)	0	0
ECOG score n(%)						
grade 0	26(33.8)	60(38.0)	86(36.6)	7(14.6)	0	0
grade 1	31 (40.3)	63(39.9)	94(40.0)	19(39.6)	0	5(62.5)
grade 2	17(22.1)	24(15.2)	41 (17.4)	19(39.6)	2(100)	3(37.5)
grade 3	0	2(1.3)	2(0.9)	1 (2.1)	0	0
missing	3(3.9)	9(5.7)	12(5.1)	2(4.2)	0	0

The median time from the diagnosis of CML AP to study entry was 1.1 months, and in the majority of patients the diagnosis of AP had been made less than 6 months from start of study. 67% of the patients had received therapy for the accelerated phase of CML, usually hydroxycarbamide (hydroxyurea). Approximately two thirds of the ALL patients were in relapse, and one third were refractory to treatment having never achieved a response (Table 35). Ten ALL patients relapsed after BMT.

Table 35 Disease history-study 0109

Disease group:	CML AP (primary group)			ALL	AML	LBC
STI571 initial dose (mg/d):	400	600	all	all doses	all doses	all doses
	N=77	N=158	N=235	N=48	N=2	N=8
Diagnosis to study entry (months)						
mean	6.5	5.7	6.0	15.6	15.3	5.7
median	1.4	0.8	1.1	8.5	15.3	4.7
range	[]
Time since diagnosis of assigned disease [n(%)]						
< 6 months	57(74.0)	118(74.7)	175(74.5)	12(25.0)	0	6(75.0)
≥6 to < 1 year	5(6.5)	18(11.4)	23(9.8)	18(37.5)	1(50.0)	1(12.5)
≥1 year to < 2 years	11(14.3)	13(8.2)	24(10.2)	10(20.8)	1(50.0)	1(12.5)
≥2 years to < 5 years	3(3.9)	8(5.1)	11 (4.7)	6(12.5)	0	0
≥5 years	1(1.3)	1(0.6)	2(0.9)	2(4.2)	0	0
Primary refractory, yes [n(%)]	na	na	na	17(35.4)	0	2(25.0)
Relapsed, yes [n(%)]	na	na	na	31 (64.6)	2(100)	6(75.0)
one relapse	na	na	na	19(39.6)	2(100)	3(37.5)
>1 relapse	na	na	na	12(25.0)	0	3(37.5)
Prior BMT [n(%)]	0	2(1.3)	2(0.9)	10(20.8)	1(50.0)	0
Prior therapy for AP [n(%)]	52(67.5)	105(66.5)	157(66.8)	na	na	na
Prior antineoplastics used for CML AP by ≥5% patients [n(%)]						
hydroxycarbamide	44(57.1)	91 (57.6)	135(57.4)			
interferon	8(10.4)	31 (19.6)	39(16.6)			
cytarabine	14(18.2)	14(8.9)	28(11.9)			
busulfan	6(7.8)	8(5.1)	14(6.0)			

Note: Percentages are based on the total number of patients in each dose group and disease group
Abbreviation: na = not applicable

7.6.4 Dosage

At the beginning of the study, STI571 was supplied in 25mg, 50mg and 100mg strength capsules but later on, only the 100mg capsule was provided. Patients usually took 400mg/d or 600mg/d once daily after breakfast, although the highest dose allowed, 800mg/d, was to be taken as 400mg bid, after breakfast and the evening meal. However, variations in this dosage regimen were permitted and occurred.

Reductions or interruptions were for safety reasons and should have followed the guidelines given in the protocol. Escalations were performed in the case of lack of efficacy when there were no safety concerns.

The changes in dose and the type of change are summarized in Table 36. In the CML AP group, a higher proportion of patients who started on 600mg/d had a dose interruption or reduction compared with those who started on 400mg/d. However, almost half of the patients whose initial dose was 400mg/d increased this dose, compared with only 12% of the patients taking 600mg/d.

Table 36 Dosage changes-study 0109

Disease group: STI571-initial dose(mg/day):	CML AP (Primary group)			ALL	AML	LBC
	400 mg	600 mg	All doses			
	N=77	N=158	N=235	N=48	N=2	N=8
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
No. of patients without change of initial dose	19(24.7)	53(33.5)	72(30.6)	22(45.8)	2(100)	4(50.0)
No. of patients with change of initial dose	58(75.3)	105(66.5)	163(69.4)	26(54.2)	0	4(50.0)
Type of change of initial dose						
Reduction	32(41.6)	85(53.8)	117(49.8)	15(31.3)	0	2(25.0)
Interruption	23(29.9)	63(39.9)	86(36.6)	5(10.4)	0	2(25.0)
Escalation	37(48.1)	19(12.0)	56(23.8)	14(29.2)	0	2(25.0)

Categories of initial dose changes are not mutually exclusive, patients may have had more than one type of dose change.

7.6.5 Patient exposure

Overall actual dose intensity for all patients in each disease group is shown in Table 37.

For each of the first 6 months, the median actual dose intensity for the CML AP patients remained at their starting dose of 400mg/d or 600mg/d indicating that the effect of dose escalations, reductions or interruptions balanced each other out so that there was no change in median actual dose intensity

For the 56 CML AP patients whose initial dose was escalated due to lack of efficacy, the overall median actual dose intensity was 459.2mg/d for the 37 patients starting on 400mg/d and 641.9mg/d for the 19 patients who started on 600mg/d. The maximum actual dose intensities for dose escalated patients occurred in month 6 (median 489.3 mg/d and 766.7mg/d).

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Table 37 Duration of exposure and dose intensity-study 0109

Disease group:	CML	AP (primary group)	ALL	AML	LBC	
Initial dose (mg/d):	400 mg	600 mg	all doses	all doses	all doses	
	N=77	N=158	N=235	N=48	N=2	N=8
Duration of exposure (days)						
mean	230.0	219.6	223.0	85.1	121.5	109.8
median	257.0	239.0	240.0	62.0	121.5	56.5
range						
n (%) patients exposed (cumulative counts)						
≥3 months	60(77.9)	137(86.7)	197(83.8)	15(31.3)	1 (50-0)	3(37.5)
≥ 6 months	49(63.6)	125(79.1)	174(74.0)	6(12.5)	0	2(25.0)
≥12 months	6(7.8)	0	6(2.6)	0	0	0
Overall actual dose intensity (mg/day)						
mean	418.86	514.85	483.40	577.33	600.00	475.63
median	400.00	578.48	480.95	600.00	600.00	461.46
25-75th percentiles	381.8-456.2	436.7-600.0	400.0-600.0	580.5-600.0	600.0-600.0	400.0-592.1
range	609.4	767.3	767.3	712.0	600.0	600.0

Note: Duration of exposure = last date of study drug - start date of study drug + 1. Interruption periods are also included in the calculation of exposure.

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7.6.6 Efficacy results

Hematologic Response

The primary outcome measure was defined as the overall confirmed hematologic response in the ITT population. Hematologic response consists of three categories: complete hematologic remission, no evidence of leukemia in blood or bone marrow without peripheral blood recovery, and return to chronic phase CML (see Section 5.2.5 of this report for definitions).

The overall hematologic response rate was 63%. A complete response was achieved in 65 patients (28%). Hematologic response rates including complete response were similar in the 400mg and 600mg dose groups (Table 38).

Table 38 Hematologic response-study 0109

STI571 initial dose (mg/day):	400 mg N=77	600 mg N=158	all doses N=235
Hematologic response [n(%)]			
overall	48(62.3)	100(63.3)	148(63.0)
95% CI	50.6-73.1	55.3-70.8	56.5-69.2
complete hematologic remission	21(27.3)	44(27.8)	65(27.7)
no evidence of leukemia	7(9.1)	20(12.7)	27(11.5)
return to chronic phase	20(26.0)	36(22.8)	56(23.8)
Absence of response			
no response	15(19.5)	23(14.6)	38(16.2)
progression	7(9.1)	17(10.8)	24(10.2)
death	2(2.6)	1 (0.6)	3(1.3)
Not assessable	5(6.5)	17(10.8)	22(9.4)

Note: Overall hematologic response complete remission + no evidence of leukemia + return to chronic phase.

Calculation of the confidence interval (CI) is based on the Pearson-Clopper formula

Not assessable was assigned to patients who only had 1 post-baseline assessment and did not discontinue due to AE or lab abnormality (classed as progression) or death.

As noted previously, one center failed a GCP audit, and the primary efficacy analysis was repeated without the 14 patients from this center. This had no relevant impact on the hematologic response rate presented here for the ITT population.

The median time to hematologic response was 1 month, ranging from 0.9 to 9.3 months. The median time to response was the same in the two dose groups: 1 month, ranging from 0.9-9.3 months and 0.9-2.9 months in the 400mg and 600mg dose groups, respectively.

Cytogenetic response

Unconfirmed responses are used in this analysis because of the intervals between bone marrow cytogenetic evaluations (monthly for first 3 months, three monthly thereafter). Overall, 50 patients (21%) achieved a major cytogenetic response (unconfirmed), including 34 patients (15%) who reached complete response. Of note, higher rates of major and complete cytogenetic response were observed in the 600mg-dose group compared to the 400mg group (Table 39).

The time to cytogenetic response is depicted in Table 40. By the time of data cut-off 8 out of the 50 (16%) patients who responded had lost their major cytogenetic response, 33 % and 11 % in the 400mg and 600mg-dose group, respectively).

Table 39 Cytogenetic response-study 0109

STI571 initial dose (mg/day):	400 mg N=77	600 mg N=158	all doses N=235
Cytogenetic response [n(%)]			
Major response (complete +partial)	12(15.6)	38(24.1)	50(21.3)
95% CI	8.3-25.6	17.6-31.5	16.2-27.1
complete	(9.1)	27(17.1)	34(14.5)
partial	5(6.5)	11 (7.0)	16(6.8)
Minor	5(6.5)	8(5.1)	13(5.5)
Minimal	9(11.7)	21 (13.3)	30(12.8)
Absence of response			
no response	32(41.6)	59(37.3)	91 (38.7)
progression without response	10(13.0)	13(8.2)	23(9.8)
death without response	2(2.6)	1(0.6)	3(1.3)
Not assessable			
Ph negative at baseline	1(1.3)	0	1(0.4)
not done	6(7.8)	18(11.4)	24(10.2)

Note: Calculation of the confidence interval is based on the Pearson-Clopper formula
 Response definition in terms of percentage of PH+ metaphases- 0% = complete; >0% ≤35% = partial; >35% -≤65% = minor; >65% -≤95% = minimal; >95% -≤100% = none.

Table 40 Time to and duration of cytogenetic response-study 0109

STI571 initial dose (mg/day):	400 mg N=77	600 mg N=158	all doses N=235
Time to major cytogenetic response (months)			
N	12	38	50
Median	2.46	2.83	2.83
95% CI	1.9-2.9	2.8-3.0	2.8-2.9
Range			
Duration of major cytogenetic response (months)			
N	12	38	50
Median	7.39	na	7.39
95% CI	4.7-7.4	4.0-na	5.7-7.4

Time to progression and overall survival

By the time of the cut-off date, 109 (69%) patients in the 600mg group were on treatment without progression, at times ranging from _____, and 49 (31 %) patients progressed at times ranging from _____. In the 400mg group, 41 (53%) progressed and the median time to progression is 10 months.

Overall, the estimated rate of patients free of progression at 9 months is 63% (95% CI 56-69%). The corresponding rate in the 400mg and 600mg groups is 52% (95% CI 41-64%) and 68% (95% CI 60-75%), respectively.

At a median follow-up of 9.8 months (based on recruitment), the estimated overall 9-month survival rate is 80% (95% CI 75-85%). The corresponding rate in the 400mg and 600mg groups is 74% (95% CI 64-84%) and 83% (95% CI 76-89%), respectively.

Cancer related symptoms and ECOG performance status

The frequencies of specified cancer related symptoms (fever, night sweats, bone pain, abdominal discomfort, arthralgia) at baseline, 3 months and 6 months are summarized in table 41.

The frequencies of the ECOG grades/scores (0 to 4) at baseline, 3 months and 6 months are summarized in table 42.

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ON ORIGINAL**

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ON ORIGINAL**

Table 41 Cancer related symptoms-study 0109

Symptom	Symptom Grade	Baseline (N=293)	3 Months (N=293)	6 Months (N=290)
Abdominal discomfort	Absent	234(79.9%)	204(69.6%)	181(62.4%)
	Grade 1	40(13.7%)	6(2.0%)	6(2.1%)
	Grade 2	13(4.4%)	1(0.3%)	0
	Grade 3	5(1.7%)	0	0
	Grade 4	0	0	0
	Progression	0	54(18.4%)	83(28.6%)
	Death	0	6(2.0%)	7(2.4%)
	Missing	1(0.3%)	22(7.5%)	13(4.5%)
	Total	293(100%)	293(100%)	290(100%)
Bone pain	Absent	241(82.3%)	200(68.3%)	180(62.1%)
	Grade 1	20(6.8%)	8(2.7%)	3(1.0%)
	Grade 2	15(5.1%)	3(1.0%)	3(1.0%)
	Grade 3	4(1.4%)	0	1(0.3%)
	Grade 4	0	0	0
	Progression	0	54(18.4%)	83(28.6%)
	Death	0	6(2.0%)	7(2.4%)
	missing	1 (0.3)	22(7.5%)	13(4.5%)
	Total	293(100%)	293(100%)	290(100%)
Arthralgia	Absent	253(86.3%)	192(65.5%)	179(61.7%)
	Grade 1	20(6.8%)	15(5.1%)	5(1.7%)
	Grade 2	15(5.1%)	3(1.0%)	2(0.7%)
	Grade 3	4(1.4%)	1(0.3%)	1(0.3%)
	Grade 4	0	0	0
	Progression	0	54(18.4%)	83(28.6%)
	Death	0	6(2.0%)	7 (2.4%)
	Missing	1(0.3%)	22(7.5%)	13(4.5%)
	Total	293(100%)	293(100%)	290(100%)
Fever	Absent	250(85.3%)	208(71.0%)	183(63.1%)
	Grade 1	36(12.2%)	2(0.7%)	4(1.4%)
	Grade 2	5(1.7%)	1(0.3%)	0
	Grade 3	1(0.3%)	0	0
	Grade 4	0	0	0
	Progression	0	54(18.4%)	83(28.6%)
	Death	0	6(2.0%)	7(2.4%)
	Missing	1 (0.3%)	22(7.5%)	13(4.5%)
	Total	293 100%)	293(100%)	290(100%)
Night Sweats	Absent	218(74.4%)	204(69.6%)	176(60.7%)
	Grade 1	55(18.8%)	7(2.4%)	10(3.4%)
	Grade 2	16(5.5%)	0	0
	Grade 3	3(1.0%)	0	1(0.6%)
	Grade 4	0	0	0
	Progression	0	54(18.4%)	83(28.6%)
	Death	0	6(2.0%)	7(2.4%)
	Missing	1(0.3%)	22(7.5%)	13(4.5%)
	Total	293(100%)	293(100%)	290(100%)

Table 42 ECOG performance status-study 0109

Treatment group	ECOG Performance score	Baseline (N=235)	3 Months (N=235)	6 Months (N=235)
All doses	Grade 0	86(36.6%)	103(43.8%)	110(46.8%)
	Grade 1	94(40.0%)	73(31.1%)	45(19.1%)
	Grade 2	41(17.4%)	10(4.3%)	12(5.1%)
	Grade 3	2(0.9%)	2(0.9%)	2(0.9%)
	Grade 4	0	0	0
	Progression	0	25(10.6%)	45(19.1%)
	Death	0	3(1.3%)	4(1.7%)
	Missing	12(5.1%)	19(8.1%)	17(7.2%)
	Total		235(100%)	235(100%)

Hematologic response in patients with increased dose

37/77 patients who initiated treatment at the 400mg-dose level had their dose increased to 600 or 800mg/day and 19/158 in the 600mg group had their dose increase to 800mg/day.

In the 400mg dose group 4/37 had a response only after dose escalation (002 0501, 003 0510, 004 0505, 009 0505). However, dose escalation in these patients occurred within the first 28 days of study start: on day 3 in two patients and days 9 and 19 in the other two. This might have occurred at the time the protocol was amended to allow therapy at an initial dose of 600mg/day and, therefore, in these patients dose escalation was not necessarily due to progression or loss of hematologic control. Seven of the remaining 33 patients maintained or achieved a second hematologic response after dose increase. In the 600mg group 4/19 patients had a response only after dose escalation (002 0509, 011 0514, 502 0514 and 505 0508). Four of the remaining 15 patients maintained or achieved a second hematologic response after dose increase.

7.7 FDA Results – Study 0109

Patient eligibility for study 0109 included four advanced Ph+ leukemia populations. Numbers of patients in each disease category are listed in Table 43.

Table 43 Eligible disease categories per FDA-study 0109

Study Population (Ph+)	N
Accelerated phase CML	235
Lymphoid blast crisis	8
Acute lymphocytic leukemia (ALL)	48
Acute myelocytic leukemia (AML)	2

7.7.1 Patient characteristics

Demographic and clinical characteristics of accelerated phase patients participating in study 0109 are indicated in Table 44. As is evident in this table patients enrolled in this study may or may not have had prior therapy for accelerated phase disease and they may have been treated with either STI-571 400 mg or 600 mg/day. The majority of study patients were performance status 0 or 1. As expected the majority of study patients had extramedullary disease and had chromosomal abnormalities in addition to the Philadelphia chromosome.

Table 44 Patient characteristics per FDA-study 0109

Characteristic	Value (N=235)
Age	
Median (range)	56 (22-86)
Sex [N (%)]	
Male	118 (50.2)
Female	117 (49.8)
Race [N (%)]	
Caucasian	210 (89.4)
Black	10 (4.3)
Other	15 (6.3)
Performance status (ECOG) [N (%)]	
0	86 (36.6)
1	94 (40.0)
2	41 (17.4)
3	2 (0.9)
Unknown	12 (5.1)
Prior accelerated phase therapy [N (%)]	
Yes	157 (66.8)
No	78 (33.2)
Chromosomal abnormalities [N (%)]	
Ph positive only	108 (46.0)
Ph pos + other chromosome abnormalities	127 (54.0)
Extramedullary disease [N (%)]	
Yes	160 (68.1)
No	75 (31.9)
STI-571 Starting Dose [N (%)]	
400 qd	77 (32.8)
600 qd	158 (67.2)

7.7.2 Hematologic response

The primary efficacy endpoint is confirmed hematologic response. As indicated in Table 45 hematologic response was further characterized as either complete, no evidence of leukemia or return to chronic phase disease. While there are 4 separate groups of patients based on the variables of prior therapy and STI-571 dose the results are not presented separately for each category because of small numbers and presumed wide confidence intervals for each result.

Hematologic response data in the FDA analysis was comparable to the sponsor's confirmed hematologic response analysis. In both analyses 148 (63%) of accelerated phase disease patients had a confirmed hematologic response. It is too early to determine response duration. In the sponsor's analysis 115 of the 148 hematologic responders were censored for response duration while in the FDA analysis 135 of the 148 responders are censored. The sponsor estimates that 84% (95% CI 78-90%) will have a response duration of at least 6 months. Preliminary FDA response duration data is indicated in the table.

There were 15 hematologic responders among patients with other categories of disease entered into trial 0109; 1/8 with lymphoid blast crisis (LBC), 12 of 48 with ALL and 2 of 2 with AML. All LBC and AML responders remain censored for response duration. Nine of the 12 ALL responders have relapsed. Median response duration for these latter patients was 84 days.

Table 45 Hematologic response per FDA-study 0109

Characteristic	N=235
Total Hematologic Responders [N (%)]	148 (63)
Best hematologic response [N (%)]	
Complete	60 (40.5)
No evidence of leukemia	27 (18.3)
Return to chronic phase	61 (41.2)
Days to hematologic response- median (range)	29 (26-334)
Censored for response duration [N (%)]	133 (90)
Current Response durations [N]	
>90d	125
>120d	112
>150d	69
>180d	53
>210d	45
>240d	18

7.7.3 Cytogenetic response

Major cytogenetic response was a secondary efficacy endpoint. Results of cytogenetic response analysis is summarized in Table 46. In FDA discussions with the sponsor it was the FDA's position that cytogenetic responses should be confirmed by a second evaluation at least one month after the initial response determination and that an adequate specimen would have at least 20 evaluable metaphases. Because of these stipulations Table 46 indicates results for all relevant subgroups. Similar to the sponsor's analysis the FDA found that 50 of 235 (21%) accelerated phase patients had at least one marrow cytogenetic evaluation that demonstrated a major cytogenetic response (MCyR). In the sponsor's analysis 68% of MCyR's had a complete cytogenetic response (CCyR). In the FDA analysis 34% of responders had a CCyR. The most likely reason for difference, based on sponsor evaluation of FDA data, is that, when serial responses varied between CR and PR, the FDA required that a majority of responses be CR before calling a patient a CCyR.

Median response duration, per FDA, cannot be determined, at present. The FDA censored a total of 44 cytogenetic responders (88%) for response duration while the sponsor censored 42 (84%). Among patients who had a major CyR, based on at least 2 cytogenetics evaluations, the FDA censored 24/24 (100%) of patients who had 20 or more metaphases evaluated on each marrow sample and 32 of 32 (100%) of patients who had less than 20 metaphases evaluated on at least one bone marrow specimen. The median duration of cytogenetic response was 7.39 months (95% CI 5.7-7.4 months) in the sponsor's analysis. As indicated above it was not determinable in the FDA analysis.

Table 46 Cytogenetic response per FDA-study 0109

	>=20 metaphases (N=50)		Irrespective of # of metaphases (N=50)	
	Confirmed*	Unconfirmed	Confirmed	Unconfirmed
Major CyR [N (%)]	24 (48)	26 (52)	32 (64)	18 (36)
Complete	10	7	10	7
Partial	14	19	22	11
Patients censored for response duration[N (%)]	24/24 (100)		32/32 (100)	

Confirmed - At least 2 marrows confirm a major cytogenetic response

Unconfirmed - Only a single marrow indicates a major cytogenetic response

In view of the importance attributed to a MCyR it was of interest to observe that patients may enter into, leave and return to major cytogenetic response status. Table 47 documents the course of one such patient. Patient 2-503 after attaining a CCyR (0% Ph+cells), lost that response on day 174 (35% Ph+cells), and then regained it on day 279.

Table 47 Variable cytogenetic response during treatment per FDA-study 0109

Patient	Study day	CyR
2-503	90	CR
	174	PR
	279	CR

7.7.4 Hematologic and cytogenetic responses

Because of the prognostic significance of both hematologic and cytogenetic response it is of interest to determine whether they track together in patients. As indicated in Table 48, 148 patients had a hematologic response and 50 had a major cytogenetic response. Of interest only 45 patients had both.

Table 48 Hematologic and cytogenetic responses per FDA-study 0109

Efficacy response	No. of Pts
HR	148
MCyR	50
CHR + MCyR	45
CHR without MCyR	103
MCyR without CHR	5

7.7.5 Symptom relief

An important aspect of treatment is symptom relief. Table 49 describes common symptoms of CML patients and indicates their severity on three sequential evaluations. While most patients listed below are asymptomatic at presentation and throughout treatment a minority have grade 1, 2 and 3 symptoms. With STI-571 treatment there appears to be a reduction in grade 1, 2 and 3 symptoms that is most evident on the day 85 evaluation but which persists on the day 169 evaluation

Table 49 Symptoms per FDA-study 0109

Visit	Symptom [N (%)]	Grade					No Data
		0	1	2	3	4	
1 d -7 to 0	Abdominal Discomfort (292)	234 (80)	40 (14)	13 (4)	5 (2)	0	0
	Arthralgia (292)	253 (87)	20 (7)	15 (5)	4 (1)	0	0
	Fever (292)	250 (86)	36 (12)	5 (2)	1 (.3)	0	0
	Night Sweats (260)	218 (75)	55 (19)	16 (5)	3 (1)	0	0
	Bone Pain (292)	241 (83)	24 (8)	19 (6)	6 (2)	2 (1)	0
22 d 85	Abdominal Discomfort (222)	204 (92)	6 (3)	1 (.5)	0	0	11 (5)
	Arthralgia (222)	192 (86)	15(7)	3 (1)	1 (.5)	0	11 (5)
	Fever (222)	208 (94)	2 (1)	1(.5)	0	0	11 (5)
	Night Sweats (222)	204 (92)	7 (3)	0	0	0	11 (5)
	Bone Pain (222)	200 (90)	8 (4)	3 (1)	0	0	11 (5)
28 d 169	Abdominal Discomfort (288)	230 (80)	15 (5)	3 (1)	3 (1)	0	36 (13)
	Arthralgia (288)	235 (82)	11 (4)	4 (1)	2 (1)	0	36 (13)
	Fever (288)	225 (78)	21 (7)	5 (2)	1 (.5)	1 (.5)	35 (12)
	Night Sweats (288)	228 (79)	17 (6)	3 (1)	2 (1)	1 (.5)	37 (14)
	Bone Pain (288)	225 (78)	10 (3)	11 (4)	6 (3)	0	36 (13)

7.7.5 Performance status changes

Performance status evaluation is shown in Table 50. For pretreatment performance status 1, 2 or 3 patients a total of 62 individuals (33%) improved their performance status (at least 2 consecutive evaluations separated by at least 1 month) during treatment.

Table 50 Performance status per FDA-study 0109

Initial P.S.	No. of Pts	Change in Performance Status N [(%)]			
		Improved	Stable	Worse	No data
0	93	--	63 (68)	24 (26)	6 (6)
1	118	33 (28)	64 (54)	13 (11)	8 (7)
2	65	29 (45)	22 (34)	5 (7)	9 (14)
3	3	3 (100)	0	0	0
Unknown	14				

8.0 Study 0110

Study no. 0110: A Phase II study to determine the efficacy and safety of STI571 in patients with chronic myeloid leukemia who are refractory to or intolerant of interferon-alpha

8.1 Study design

This was a Phase II, open-label, non-randomized, single-treatment, multi-center trial. During the core phase of the study, patients received STI571 at a dose of 400 mg daily for up to 12 months. Patients completing 12 months of therapy were eligible to continue treatment in the extension phase of the study provided that, in the opinion of the investigator, they had benefited from treatment with STI571 and had no safety concerns. All patients will be followed for survival for up to 5 years.

Justification for a non-randomized trial in the CML populations included and defined in this trial is based on its poor prognosis and on the lack of a generally accepted standard of medical care. The 400-mg daily dose chosen was one that is both (1) sufficiently higher than the 300 mg daily dose so as to offer a reasonable margin of error in terms of achieving blood levels that have been associated with efficacy in the phase I trial and (2) sufficiently lower than the 600 mg daily dose so as to avoid exposure of patients with a substantially better prognosis than the only dose level associated to date with drug-related mortality (600 mg).

The target population was to include a minimum of 150 adult patients with Ph+ CML who were hematologically resistant or refractory to IFN and otherwise eligible for treatment with STI571, as well as 100 patients eligible for STI571 treatment who were cytogenetically resistant or refractory to IFN. It was planned that approximately 100 patients with IFN intolerance would also be included.

8.2 Inclusion and exclusion criteria

Inclusion Criteria

Patients included in the study were:

- Males or females 18 years of age.
- Ph+ and in the chronic-phase of the disease.
- With a documented failure of IFN or an IFN-containing therapy, characterized as resistance or refractoriness defined as any of the following:
 - a) **Hematologic Resistance** - Failure to achieve a CHR, lasting for at least 1 month despite 6 or more months of IFN or an IFN-containing regimen, in which IFN was administered at a dose of at least 25 million international units (MIU) per week. During this treatment period the cumulative duration of hydroxyurea therapy may not have exceeded 50% of the treatment period with the IFN-containing regimen.
 - b) **Cytogenetic Resistance** - Bone marrow cytogenetics showing 65% Ph+ after one year of IFN-based therapy,
 - c) **Cytogenetic Refractoriness** - An increase in the Ph+ chromosome bone marrow cells by at least 30 percentage points (e.g. from 20% to 50%, or from 30% to 60%) confirmed by two samples at least 1 month apart, or an absolute increase to 65%.
 - d) **Hematologic Refractoriness** - A rising WBC count (to a level $20 \times 10^9/L$, confirmed by two samples taken at least two weeks apart) for patients achieving a complete hematologic response while receiving IFN or an IFN-containing regimen. This regimen must have included IFN at a dose of at least 25 million international units (MIU) administered per week. During this treatment period the cumulative duration of hydroxyurea therapy may not have exceeded 50% of the treatment period with the IFN-containing regimen. For purposes of this report all refractory populations will be referred to as "relapsed" populations
- With a documented intolerance to IFN therapy defined as a Grade 3 non-hematologic toxicity persisting for at least one month, for patients receiving IFN or an IFN-containing regimen. IFN was to be administered at a dose of at least 25 MIU/week. Patients who were intolerant of IFN were to have been diagnosed ≥ 6 months from the time of entry into the study.
- With written voluntary informed consent.

Exclusion criteria

Patients excluded from the study were:

- Of childbearing potential without a negative pregnancy test prior to the initiation of study drug. Barrier contraceptive precautions are to be used throughout the trial in both sexes.

- With serum bilirubin and creatinine concentrations more than twice the upper limit of the normal range (ULN)
- With SGOT and SGPT more than twice the ULN
- With percentage of blasts or basophils in blood or marrow >15%
- With percentage of blasts plus promyelocytes in blood or marrow ~30%
- With a platelet count <100 x 10⁹/L
- With an ECOG Performance Status Score ≥ 3
- Receiving busulfan within 6 weeks of Day 1
- Receiving treatment with IFN or cytosine arabinoside (Ara-C) within 14 days of Day 1
- Receiving treatment with hydroxyurea within 7 days of Day 1
- Receiving other investigational agents within 28 days of Day 1
- With New York Heart Association class III or IV heart failure
- With a history of non-compliance to medical regimens or potentially unreliable
- With prior marrow or stem cell transplantation

8.3 Amendments

There were two amendments to the original study protocol dated 05 November 1999. None of the amendments affected the integrity of the data or the validity of the results and all appropriate sections of this report reflect the changes. The key changes for Amendment 01 dated 13 December 1999 are described below; These changes were to:

Clarify the definition of the IFN-refractory patient population.

Include patients with a documented hematologic resistance to an IFN-containing regimen.

Revise the statistical analysis for the inclusion of patients with a documented hematologic resistance to an IFN-containing regimen.

Add two additional sampling timepoints to the full PK profile to more accurately evaluate the profile of STI571.

Expand the time for the screening bone marrow examination from within one week of study start to within one month.

The key changes for Amendment 02 dated 12 September 2000 are described below; These changes were to:

Clarify dose interruptions/reductions for Grade 3/4 hematologic toxicity (as outlined in letter to investigators dated 24 April 2000).

Revise the guidelines for oral administration of STI571 relative to breakfast, and specify that STI571 may be administered before, during or after meals. A preliminary study of the effect of food on the bioavailability of STI571 indicated that when administered with food there was a minimal impact on the bioavailability of STI571, which did not achieve statistical significance.

Clarify visit schedule (Extension Phase) specifically for bone marrow exams. In the extension phase bone marrows are due every 12 weeks, therefore, the first bone marrow should be done on Week 61, not Week 55.

Update patient informed consent to include changes to administration of STI571 and evolving STI571 safety profile.

Additionally, an amendment designed to evaluate the effects on the bioavailability of STI in Study 109 was conducted in Center 004 to assist with completion. The amendment was designed to evaluate the effect of a standardized high-fat meal on the pharmacokinetic parameters of orally administered STI571. A total of six patients were randomized into either treatment sequence A, or B of a two-way crossover study design (A = "fasted"- "fed" or B = "fed"- "fasted"). Therefore, for Center 004 Amendment 02 was this food effect study and the above Amendment 02 became Amendment 03 (Center 004 only).

8.4 Statistical methods

Data are summarized with respect to demographic and baseline characteristics, efficacy and safety observations and measurements. The following sections describe the variables and methods that were used, and reference the relevant post-text table in which the data are summarized. All summary tables and listings are presented by disease group: hematologic failure, cytogenetic failure, IFN intolerant, and overall (all disease groups combined). Despite the protocol specification that all patients were to begin receiving study drug at a fixed dose of 400 mg daily, a total of eight patients started treatment with a dose of 600 mg daily. In order to use standard programs within the project, the listings are presented by initial dose (400 mg or 600 mg). All summary tables are done for all doses together.

It was planned that the data from all centers that participated in this protocol would be combined, so that an adequate number of patients would be available for analysis.

Populations

Intent-to-treat (ITT) population consists of all enrolled patients. The **safety population** consists of all patients who received at least one dose of study medication. As all patients enrolled were also treated the ITT and Safety populations are identical. **Per protocol (PP)** population is a subset of the ITT population without major violations of the protocol (i.e. violations likely to significantly compromise the design of the study as regards the assessment of the drug's efficacy for patients in chronic phase of CML as defined in the protocol).

Major protocol violations. taken as disqualifying patients from the PP populations were as follows:

For hematologic and cytogenetic response assessments

- patients not in the appropriate phase of CML as defined in the protocol
- failure to document Ph chromosome positivity
- administration of prescribed antineoplastic drugs during treatment with STI571 (hydroxyurea for more than one week, or ARA-C, interferon, busulfan, anthracyclines for any period of time).

For hematologic response assessment only

- absence of two post-baseline efficacy assessments