

#### **For cytogenetic response assessment only**

- absence of at least one post-baseline bone marrow cytogenetic assessment in patients not dying or discontinuing treatment because unsatisfactory therapeutic effect.
- documented Ph chromosome negativity or missing at baseline (followed by Ph chromosome negative assessment thereafter).

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  $\geq 3$
- insufficient wash-out period for prior antineoplastics (as defined in Section 3.3.2.)

#### **Deviations from the protocol**

The protocol 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 the ITT population, 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 underwent a minimum of nine months of therapy without any major deviations from the protocol procedures.

#### **Efficacy evaluation**

The primary efficacy variable in this trial was the rate of complete and major cytogenetic response (See section 5.2.5 for definitions).

As the follow-up time in this study was short 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.

The cytogenetic response was calculated for the ITT and PP populations.

According to Fleming's single stage procedure, the success criterion for patients with hematologic failures was considered to have been reached when 21/132 responders were seen (i.e. the lower limit of the 95% exact confidence interval for the confirmed hematologic response rate exceeded 10%). For patients with cytogenetic failures, the success criterion was considered to have been reached when 19/79 responders were seen (i.e. the lower limit of the 95% exact confidence interval for the confirmed hematologic response rate exceeded 15%)

#### **Secondary efficacy variables**

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 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.

For duration of complete cytogenetic response the same procedure was used as given above for duration of major response with a loss of response defined as an increase to >0% Ph+ cells. Duration of cytogenetic responses was evaluated using Kaplan-Meier methods.

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.

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

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 10<sup>9</sup>/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.

According to the protocol, loss of complete hematologic response was defined as a rising WBC count (increased to a level above the ULN at the laboratory where the analysis was performed, confirmed by two samples obtained one month apart) or death due to any cause. According to the FDA (20 September 2000) no confirmation is needed for 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 ( 30% blasts in PB or BM, extramedullary disease other than liver/spleen enlargement)
- discontinuation due to 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 accelerated phase: This duration was calculated for all patients as the time between start of treatment and the earliest date of the following:

- progression to accelerated phase ( 15%-<30% blasts in PB or BM, 30% blasts + promyelocytes in PB or BM, 20% basophils in PB)
- progression to blast crisis ( 30% blasts in PB or BM, extramedullary disease other than liver/spleen enlargement)
- discontinuation due to unsatisfactory therapeutic effect or death. For patients who never responded, progression to accelerated phase was taken to be the date of their

first post-baseline assessment consistent with accelerated phase/blast crisis. For patients who were in accelerated phase or blast crisis at study entry and responded during therapy, progression to accelerated phase 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 complete hematologic response
- progression to accelerated phase or blast crisis
- discontinuation due to unsatisfactory therapeutic effect or death. This variable was not specified in the protocol but was calculated as additional analysis.

**Overall survival:** 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 endpoint's:**

- ECOG performance status and cancer related symptoms
- The Ph chromosome was also evaluated by fluorescent in situ hybridization (FISH). Cytogenetic and FISH results are listed and summarized side by side.

Planned and actual sample size success criteria for cytogenetic response in patients with prior hematologic or cytogenetic failures are recorded in **Table 51**.

**Table 51 Cytogenetic response success criteria-study 0110**

Sample	Sample size	Min. no	p0	p1	P	95% CI t
		Responders				
<b>Hematologic failures</b>						
Planned	132 (minimum)	21	10%	20%	15.9%	10.1-23.3%
Actual	152	24	10%	20%	15.8%	10.4-22.6%
<b>Cytogenetic failures</b>						
Planned	79 (minimum)	19	15%	30%	24.1%	15.1-35.0%
Actual	186	39	15%	30%	21.0%	15.4-27.5%

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

In addition, it was also planned to evaluate the rate of cytogenetic response and safety for patients who were IFN intolerant. The sample size calculation was based on practical considerations and was set to 100.

## 8.5 Clinical study results per sponsor

### 8.5.1 Patient disposition

In the period between 6 December 1999 and 30 May 2000 a total of 532 patients with the diagnosis of CML were recruited onto the study. These patients were entered through 28 centers in Switzerland, France, Germany, Italy, the UK and the USA. Of these 532 patients, 152 (28.6%) were in hematologic failure, 186 (34.9%) were in cytogenetic failure and a further 194 patients (36.5%) were IFN intolerant. Table 52 provides details of the disposition of the patients at the time of data cut-off (30 October 2000).

According to protocol, patients were admitted into one of four categories of documented resistance or relapse to interferon. The categories are defined as: hematologic resistance (n=75, 14.1%), cytogenetic resistance (n=138, 25.9%), cytogenetic relapse (n=48, 9.0%), and hematologic relapse (n=77, 14.5%). For this report and the corresponding tables, patients have been pooled into two main categories based on their diagnosis following failure of IFN therapy: hematologic failure (hematologic resistance + hematologic relapse) or cytogenetic failure (cytogenetic resistance + cytogenetic relapse). The interferon intolerant patients are categorized separately.

**Table 52 Patient disposition-study 0110**

Disease Group	Hematologic Failure n=152	Cytogenetic Failure n=186	IFN Intolerant n=194	Overall n=532
Number (%) of patients				
Enrolled	152(100%)	186(100%)	194(100%)	532(100%)
Ongoing	142(93.4%)	176(94.6%)	179(92.3%)	497(93.4%)
Discontinued	10(6.6%)	10(5.4%)	15(7.7%)	35(6.6%)
Reason for discontinuations	10(6.6%)	10(5.4%)	15(7.7%)	35(6.6%)
Adverse event(s)	2(1.3%)	2(1.1%)	4(2.1%)	8(1.5%)
Unsatisfactory effect	6(3.9%)	6(3.2%)	10(5.2%)	22(4.1%)
Protocol violation	0	1(0.5%)	1(0.5%)	2(0.4%)
Subject withdrew consent	0	1(0.5%)	0	1(0.2%)
Administrative problems	1(0.7%)	0	0	1(0.2%)
Death	1(0.7%)	0	0	1(0.2%)

There were no marked differences in the numbers of patients prematurely discontinued from the study between the disease groups, nor were there any differences in the reasons for premature discontinuation between the three groups.

### 8.5.2 Major Protocol deviations

It should be noted that although the protocol required that all patients were to have been treated with a daily dose of 400 mg STI571, in one center in Germany (010) and one in Italy (011) a total of eight patients were treated with a beginning dose of 600 mg daily. Although data are presented separately for the two dose groups in the listings, in the

tables and in the body of the report the data from all treated patients have been grouped together irrespective of the dose of STI571 administered.

Protocol violations were designated minor or major. They are summarized in Table 53. A total of 38.8% (59/152) of patients from the hematologic failure group and 29.0% (54/186) of patients from the cytogenetic failure group were found to have any protocol violations.

The major protocol violations are those that would have affected either or both the hematologic and cytogenetic efficacy analyses so that patients with these violations were excluded from the PP populations. The major violations comprised for the most part incorrect assignment to disease group or prohibited medications. A total of 86 patients (16.2%) were excluded from all PP efficacy analyses due to major protocol violations. It should be noted that some patients had more than one protocol violation and may have been excluded from more than one PP efficacy analysis.

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**Table 53 Protocol violations-study 0110**

Disease Group	Hematologic	Cytogenetic	IFN	Overall
	Failure	Failure	Intolerant	
	n=152	n=186	n=194	n=532
	n(%)	n (%)	n (%)	n(%)
Protocol Violations				
No. of patients with violations	59(38.8%)	54(29.0%)	58(29.9%)	171(32.1%)
Excluded from all PP efficacy analyses	24(15.8%)	30(16.1%)	32(16.5%)	86(16.2%)
Ph chromosome negative at baseline	1(0.7%)	0	0	1(0.2%)
Not in the disease group as defined in the protocol	19(12.5%)	28(15.1%)	31(16.0%)	78(14.7%)
Myeloid blast crisis	14(2.6%)	3(1.6%)	5(2.6%)	12(2.3%)
Accelerated phase	1 (0.7%)	10(5.4%)	6(3.1%)	17(3.2%)
Not assigned	14(9.2%)	15(8.1%)	20(10.3%)	49(9.2%)
Forbidden antineoplastics during study	5(3.3%)	2(1.1%)	2(1.0%)	9(1.7%)
Excluded from PP analysis (Hematologic Response)	4(2.6%)	1 (0.5%)	5(2.6%)	10(1.9%)
<2 post-baseline efficacy assessments for hematological response (and no PD/cleath)	4(2.6%)	1(0.5%)	5(2.6%)	10(1.9%)
Excluded from PP analysis (Cytogenetic Response)	24(15.8%)	17(9.1%)	14(7.2%)	55(10.3%)
Ph chromosome negative at baseline	3(2.0%)	1 (0.5%)	1 (0.5%)	5(0.9%)
No post-baseline efficacy assessments for cytogenetic response (and no PD/death)	21 (13.8%)	16(8.6%)	13(6.7%)	50(9.4%)
Minor Protocol Violations	27(17.8%)	19(10.2%)	22(11.3%)	8(12.8%)
Interferon-alpha within 48 hours of day 1	13(8.6%)	7(3.8%)	4(2.1%)	24(4.5%)
Cytosine arabinoside within days of day 1	7 1 (0.7%)	3(1.6%)	1 (0.5%)	5(0.9%)
Busulfan within six weeks of day 1	1 (0.7%)	0	1 (0.5%)	2(0.4%)
Hydroxyurea within 7 days of day 1	7(4.6%)	3(1.6%)	10(5.2%)	20(3.8%)
No documentation of Ph chromosome positivity (Ph missing at baseline)	8(5.3%)	6(3.2%)	6(3.1%)	20(3.8%)
SGOT (AST) >3 x ULN	1 (0.7%)	0	1 (0.5%)	2(0.4%)
SGPT (ALT) >3 x ULN	4(2.6%)	1 (0.5%)	0	5(0.9%)

Note: Patients may be in more than one category

### 8.5.3 Baseline demographics and background characteristics

The total numbers of patients in each analysis population are summarized in Table 54.

**Table 54 Baseline characteristics-study 0110**

Disease Group	Hematologic Failure n=152 n (%)	Cytogenetic Failure n=186 n (%)	IFN Intolerant n=194 n (%)	Overall n=532 n (%)
Population				
Efficacy (ITT)	152(100%)	186(100%)	194(100%)	532(100%)
Safety	152(100%)	186(100%)	194(100%)	532(100%)
Efficacy PP (for cytogenetic response evaluation)	111 (73.0%)	145(78.0%)	150(77.3%)	406(76.3%)
Efficacy PP (for Hematologic response evaluation)	125(82.2%)	156(83.9%)	160(82.5%)	441 (82.9%)

The ITT and safety populations were identical and included all patients enrolled into the study. The PP populations included patients who met the criteria for one of the Ph+ CML disease sub-types defined in the inclusion criteria, without any major deviations from the protocol procedures. In the hematologic failure group, ITT patients (73% of the entire group) were included in the cytogenetic response PP efficacy analysis. 145 (78%) and 150 (77%) were included in the cytogenetic response PP efficacy analysis from the cytogenetic failure and IFN intolerant groups, respectively. Overall, more than 80% of each disease group were eligible for inclusion in the hematologic response PP efficacy analysis.

Table 55 summarizes the baseline demographic characteristics of the patients in the different disease groups.

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**Table 55 Baseline demographics-study 0110**

Disease Group	Hematologic Failure n=152	Cylogenetic Failure n=186	IFN Intolerant n=194	Overall n=532
<b>Age (years)</b>				
mean	52.5	52.4	57.1	54.2
sd	13.88	12.41	12.41	13.02
median	56.0	53.0	59.0	57.0
range	18-79	23-77	20-90	18-90
<b>Age category</b>				
<50 years	56(36.8%)	64(34.4%)	48(24.7%)	168(31.6%)
50 to < 60 years	38(25.0%)	64(34.4%)	51(26.3%)	153(28.8%)
60 to < 70 years	47(30.9%)	44(23.7%)	68(35.1%)	159(29.9%)
70 years	11(7.2%)	14(7.5%)	27(13.9%)	52(9.8%)
<b>Sex</b>				
Male	103(67.8%)	110(59.1%)	98(50.5%)	311(58.5%)
Female	49(32.2%)	76(40.9%)	96(49.5%)	221(41.5%)
<b>Race</b>				
Caucasian	128(84.2%)	159(85.5%)	176(90.7%)	463(87.0%)
Black	13(8.6%)	10(5.4%)	9(4.6%)	32(6.0%)
Oriental	3(2.0%)	3(1.6%)	2(1.0%)	8(1.5%)
Other	8(5.3%)	14(7.5%)	7(3.6%) <sup>2</sup>	9(5.5%)
<b>Body surface area (M)</b>				
n	147	184	190	521
mean	1.94	1.92	1.89	1.92
sd	0.245	0.257	0.223	0.242
median	1.93	1.92	1.90	1.91
range	1.40-2.76	1.12-2.80	1.45-2.80	1.12-2.80
<b>ECOG performance status</b>				
Grade 0	101(66.4%)	117(62.9%)	96(49.5%)	314(59.0%)
Grade 1	44(28.9%)	53(28.5%)	75(38.7%)	172(32.3%)
Grade 2	5(3.3%)	3(1.6%)	10(5.2%)	18(3.4%)
Missing	2(1.3%)	13(7.0%)	13(6.7%)	28(5.3%)

**Table 56** summarizes the relevant medical history of the patients in each disease group in the ITT population. This shows that the percent of patients within the subsets for duration of disease, time from diagnosis and specific prior therapies were the same for all disease groups. Patients had lived an average of more than 3 years with the diagnosis of CML, although patients with only three months from diagnosis, as well as those with more than 10 years from initial diagnosis, were included on the study. The great majority of patients were in late chronic phase CML, defined as being more than 12 months after their initial diagnosis.

Patients had received a median of 14 months of prior IFN given at a dose equal to or higher than 25 MIU/week (75% of patients received this for a duration of 7 months or more). As expected given the definitions of the different disease groups, the duration of prior IFN was shorter for the IFN intolerant patients (7.1 months) as compared to the hematologic failure patients (12.1 months) and the cytogenetic failure patients (22 months).

**Table 56 Relevant medical history-study 0110**

Disease Group	Hematologic Failure n=152	Cytogenetic Failure n=186	IFN intolerant n=194	Overall n=532
Time since first diagnosis of CML (mo)				
median	32.9	32.7	29.6	32.0
range	3-131	10-184	3-218	3-218
Time since first diagnosis of CML				
<6 months	1(0.7%)	0	4(2.1%)	5(0.9%)
6 to <12 months	20(13.2%)	2(1.1%)	22(11.3%)	44(8.3%)
12 to <24 months	37(24.3%)	51(27.4%)	57(29.4%)	145(27.3%)
2 years to <5years	67(44.1%)	88(47.3%)	71(36.6%)	226(42.5%)
5 years	27(17.8%)	45(24.2%)	40(20.6%)	112(21.1%)
Duration of prior IFN at dose 25 MIU/week				
n	152	186	189	527
median (months)	12.1	22	7.1	14
25th -75th %	7-25	14-43	3-15	7-27
range	1-83	4-135	0-117	0-135
Any prior anti-neoplastic therapy	152(100%)	186(100%)	194(100%)	532(100%)
Prior antineoplastics used in IFN containing regimens				
Hydrea	144(94.7%)	160(86%)	180(92.8%)	484(91.0%)
Ara-C	75(49.3%)	104(55.9%)	94(48.5%)	273(51.3%)
Homoharringtonine	6(3.9%)	45(24.2%)	21 (10.8%)	72(13.5%)
IFN monotherapy	4(2.6%)	10(5.4%)	7(3.6%)	21 (3.9%)
Other	24(15.8%)	49(26.3%)	36(18.6)	109(20.5%)

Table 57 provides details of the disease characteristics and major prognostic variables for each of the disease groups at baseline. As expected from the protocol selection criteria, patients in the hematologic failure group had a higher frequency of extramedullary disease, higher baseline WBC and platelet counts and a higher percentage of blasts and early forms in the peripheral blood.

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**Table 47. Baseline disease characteristics-study 0110**

Disease Group	Hematologic Failure n=152	Cytogenetic Failure n=186	IFN Intolerant n=194	Overall n=532
Extramedullary involvement	51 (33.6%)	36(19.4%)	42(21.6%)	129(24.2%)
Splenomegaly				
>0 to <5 cm	24(15.8%)	19(10.2%)	18(9.3%)	61 (11.5%)
5 to <10 cm	14(9.2%)	4(2.2%)	6(3.1%)	24(4.5%)
10 cm	4(2.6%)	4(2.2%)	4(2.1%)	12(2.3%)
Hepatomegaly				
>0 to <5 cm	14(9.2%)	10(5.4%)	13(6.7%)	37(7.0%)
5 to <10 cm	3(2.0%)	1 (0.5%)	3(1.5%)	7(1.3%)
10 cm	1 (0.7%)	0	0	1 (0.2%)
Lymph node	4(2.6%)	2(1.1%)	5(2.6%)	11 (2.1%)
Other	0	1 (0.5%)	0	1 (0.2%)
WBC (x10 <sup>9</sup> /L)				
median	29.55	10.45	11.60	14.27
range				
Platelets (x10 <sup>9</sup> /L)				
median	351.00	57.50	313.50	295.50
range				
Hemoglobin (g/L)				
median	124.00	122.50	125.00	124.00
range				
Early forms + Blasts (%)				
median	12.00	3.00	2.00	5.00
range				
Basophils (%)				
median	3.00	2.00	2.00	2.00
range				
Other chromosomal abnormalities				
No	118(77.6%)	153(82.3%)	149(76.8%)	420(78.9%)
Yes	24(15.8%)	26(14.0%)	37(19.1%)	87(16.4%)
Missing	10(6.6%)	7(3.8%)	8(4.1%)	25(4.7%)

As noted, patients who had either hematologic relapse or resistance were combined into the disease group hematologic failure, and those that had cytogenetic resistance or relapse were combined within the cytogenetic failure disease group. However, evaluations of the baseline and disease characteristics of the individual subgroups were performed.

Out of the 75 patients with hematologic resistance, 8% were reported to have had some documentation of response to IFN, however only 1 patient was reported to have had a response sustained more than 1 month. The majority of these patients (69, 92%) had never achieved a complete hematologic response.

Patients classified as having hematologic relapse (n=77) required an elevated WBC to qualify for this subgroup. For these patients, increases were recorded at a median of 6.7 months prior to study entry (25th -75th percentiles 2-19.1).

Among the 138 patients with cytogenetic resistance, 123 had 65% Ph+ metaphases (89.1%) and only two had less than 65% Ph+ metaphases after 1 year of IFN therapy, while 13 had missing values. During the history of their disease, some patients were reported to have achieved some level of cytogenetic response. Thus, 12 patients (8.7%) were reported to have had at least one assessment in which there were <65% Ph+ metaphases.

A total of 48 patients entered the study categorized as in cytogenetic relapse. Their best response while undergoing IFN therapy was classified as a major response in 30 (62.5%), a minor response in 11 (22.9%), and a minimal or no response in 2 (4.2%) and 1 (1%), respectively. Evidence for cytogenetic relapse before study entry was seen at  $\geq 12$  months in 93.8% of these patients.

For the group of IFN intolerant patients (n=194), the events required to qualify for this disease group included at least one month with a documented non-hematologic toxicity of at least Grade 3 severity. These events occurred during the first month of IFN in 29.9%, between month 1 and 3 in 16.5% and at or beyond 3 months of IFN in 49%. The time from the start of the IFN intolerance to study entry was more than 12 months in 54.6% of patients, 6 to 12 months in 20.1% of patients and less than 6 months in 23.2% of patients.

#### **8.5.4 Dosage**

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. One study center in Germany (010) enrolled five patients and one center in Italy (011) enrolled three patients beginning at the 600-mg dose.

Table 58 shows that 36.6% to 50% of patients did not require a change in dosage throughout the study. As specified in the protocol, the majority of other dose changes were secondary to safety concerns (AE or lab abnormality) or lack of efficacy. It should be noted that for some patients, several changes (escalation, reduction and/or interruption) occurred.

**Table 58 Dose changes-study 0110**

<b>Disease Group</b>	<b>Hematologic Failure n=152</b>	<b>Cytogenetic Failure n=186</b>	<b>IFN Intolerant n=194</b>	<b>Overall n=532</b>
No. of patients without dose changes	76(50.0%)	68(36.6%)	78(40.2%)	222(41.7%)
No. of patients with dose changes	76(50.0%)	118(63.4%)	116(59.8%)	310(58.3%)
Change of initial dose				
Reduction	52(34.2%)	103(55.4%)	86(44.3%)	241 (26.5%)
Escalation	21 (13.8%)	9(4.8%)	13(6.7%)	43(8.0%)
Interruption	46(30.3%)	83(44.6%)	79(40.7%)	208(39.0%)
Reason for dose change				
AE or lab abnormality	47(30.9%)	94(50.5%)	89(45.9%)	230(43.2%)
Lack of efficacy	14(9.2%)	6(3.2%)	6(3.1%)	26(4.9%)
AE or lab abnormality/ Lack of efficacy	5(3.3%)	3(1.6%)	6(3.1%)	14(2.6%)
Other	10(6.6%)	15(8.1%)	15(7.7%)	40(7.5%)

### 8.5.5 Patient exposure

Duration of exposure is summarized in Table 59. By the cut-off date of 30-Oct-00 all patients had the possibility of receiving treatment for at least 5 months. The overall patient population was exposed to study drug for a median of 254 days (range 16-320 days), and more than 86% received drug for at least six months. As recruitment was slower for the hematologic failure group, the duration of exposure was somewhat lower, i.e. only 61.8% of patients received drug for at least 6 months in comparison to 97% and 95% of patients in the cytogenetic failure and IFN intolerant groups, respectively. An assessment of the actual dose intensity was performed on all disease groups. As discussed, this was calculated as the cumulative dose divided by the cumulative duration of treatment. The mean and median dose per day actually received by patients on the study was strikingly similar for all disease groups in which the majority received the 400 mg dose daily, thus despite dose changes in over 58% of patients (Table 59), the calculated drug exposure was not substantially affected.

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**Table 59 Duration of drug exposure-study 0110**

Disease Group	Hematologic Failure n=152	Cytogenetic Failure n=186	IFN Intolerant n=194	Overall n=532
<b>Duration of exposure (days)</b>				
mean	207.9	270.1	253.9	246.4
sd	54.14	39.90	41.98	51.67
median	210.0	272.5	254.0	254.0
range				
<b>Duration of exposure</b>				
<3 months	5(3.3%)	3(1.6%)	5(2.6%)	13(2.4%)
3 months - <6 months	53(34.9%)	2(1.1%)	5(2.6%)	60(11.3%)
6 months - <12 months	94(61.8%)	181 (97.3%)	184(94.8%)	459(86.3%)
<b>Time since recruitment (days)</b>				
mean	233.1	297.7	284.8	274.5
sd	46.73	21.32	18.96	40.33
median	234.0	300.0	280.0	281.0
range				
<b>Time since recruitment</b>				
3 months - <6 months	33(21.7%)	2(1.1%)	0	35(6.6%)
6 months - <12 months	119(78.3%)	184(98.9%)	194(100%)	497(93.4%)
<b>Actual dose intensity (mg/d)</b>				
mean	386.8	355.5	375.9	371.9
sd	70.1	82.1	75.6	77.4
median	400.0	394.9	398.2	398.7
range				

### 8.5.5 Efficacy results

As was noted, with only a short follow-up time most patients (48%) had only one or two available bone marrow cytogenetic assessments for evaluation of efficacy. Fifty-three patients (10%) had no post-baseline assessment at all and 222 patients (42%) had 3 post-baseline cytogenetic assessments (Table 60).

**Table 60 Number of cytogenetic assessments post baseline-study 0110**

# Post Baseline BM assessments	# Patients	%	Cumulative # Patients	Cumulative % Patients
0	53	10.0	53	10.0
1	93	17.5	146	27.4
2	163	30.6	309	58.1
3	222	41.7	531	99.8
4	1	0.2	532	100.0

Table 61 shows the primary response results for all groups included in the ITT population. With regard to the unconfirmed responses, the rates of major and complete responses were 49.4% (CI95% [45.4%, 53.4%]) and 30.1% (CI95% [26.1%, 34.1%]) respectively for all disease groups combined.

In the two target disease groups the success criteria were fulfilled: The rates of major and complete responses for the hematologic failure group were 36.2% (CI95% 28.6-44.4) and 20.4% (CI95% 14.3-27.7), respectively. As expected, these rates were somewhat better for both the cytogenetic failure group with unconfirmed major and complete responses of 51.1% (CI95% 43.7-58.5), and 30.1% (CI95% 23.6-37.2) respectively. An exploration of unconfirmed cytogenetic response in the IFN intolerant group revealed somewhat higher responses for this group (Table 9-2).

The rates of the confirmed major and complete responses were also calculated. These rates for the overall ITT population were 38.0% (CI95% 33.8-42.2) and 14.7% (CI95% 11.8-18.0), respectively for all disease groups combined. The corresponding rates for the hematologic failure group were 21.7% (CI95% 15.4-29.1) and 5.3% (CI95% 2.3-10.1). Thus, despite more than one quarter of the patients not having confirmation of responses by the cut off date, the success criteria had already been achieved.

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**Table 61 Cytogenetic response-study 0110**

Response	Cytogenetic Response			
	Unconfirmed Response n (%)	95 % CI	Confirmed Response n (%)	95 % CI
<b>Overall n=532</b>				
Major (CR+PR)	263(49.4%)	45.1 -53.8	202(38.0%)	33.8-42.2
Complete	160(30.1%)	26.2-34.2	78(14.7%)	11.8-18.0
Partial	103(19.4%)	16.1-23.0	124(23.3%)	19.8-27.1
Minor	30(5.6%)		32(6.0%)	
Minimal	63(11.8%)		38(7.1%)	
None	121 (22.7%)		111 (20.9%)	
Not done	50(9.4%)		135(25.4%)	
Progression 3(0.6%)	12(2.3%)			
Ph- at baseline	2(0.4%)		2(0.4%)	
<b>Hematologic Failure n=152</b>				
Major (CR+PR)	55(36.2%)	28.6-44.4	33(21.7%)	15.4-29.1
Complete	31(20.4%)	14.3-27.7	8(5.3%)	2.3-10.1
Partial	24(15.8%)	10.4-22.6	25(16.4%)	10.9-23.3
Minor	8(5.3%)		8(5.3%)	
Minimal	23(15.1%)		10(6.6%)	
None	41(27.0%)		34(22.4%)	
Not done	21 (13.8%)		61 (40.1%)	
Progression	2(1.3%)		4(2.6%)	
Ph- at baseline	2(1.3%)		2(1.3%)	
<b>Cytogenetic Failure n=186</b>				
Major (CR+PR)	95(51.1%)	43.7-58.5	76(40.9%)	33.7-48.3
Complete	56(30.1%)	23.6-37.2	29(15.6%)	10.7-21.6
Partial	39(21.0%)	15.4-27.5	47(25.3%)	19.2-32.1
Minor	15(8.1%)		14(7.5%)	
Minimal	21 (11.3%)		15(8.1%)	
None	38(20.4%)		39(21.0%)	
Not done	16(8.6%)		40(21.5%)	
Progression	1(0.5%)		2(1.1%)	
Ph- at baseline	0		0	
<b>IFN Intolerant n=194</b>				
Major (CR+PR)	113(58.2%)	51.0-65.3	93(47.9%)	40.7-55.2
Complete	73(37.6%)	30.8-44.9	41 (21.1%)	15.6-27.6
Partial	40(20.6%)	15.2-27.0	52(26.8%)	20.7-33.6
Minor	7(3.6%)		10(5.2%)	
Minimal	19(9.8%)		13(6.7%)	
None	42(21.6%)		38(19.6%)	
Not done	13(6.7%)		34(17.5%)	
Progression	0		6(3.1%)	
Ph- at baseline	0		0	

Additionally, evaluation of the response rates by baseline characteristics in the overall ITT population showed a higher rate of response in patients with ECOG performance status <2, hemoglobin  $\geq 100$  g/L, WBC <  $50 \times 10^9/L$ , and platelets  $\geq 100 \times 10^9/L$ . Of note, there was no substantial difference in response rates by age group. Of the patients who were diagnosed <12 months prior to study entry, 67.3% (33/49) responded, whereas 47.6% (230/483) of patients responded who were diagnosed  $\geq 12$

months before recruitment. Responders included 51.8% (161/311) of the males entered onto the study and 46.2% (102/221) of the females entered onto the study.

### Time to and duration of cytogenetic responses

More than 50% of the patients with major cytogenetic response achieved their response within 3 months (median = 2.9 months). The last major response was achieved after 8.8 months. The time to major and complete cytogenetic responses was similar in the three disease groups.

The duration of major cytogenetic responses was not substantially different between the disease groups, with no disease group yet achieving a median duration of response. At cut-off, 10 patients had relapsed at times ranging from ( ) Of these 10 patients, one was a hematologic failure, 3 were cytogenetic failures and 6 were IFN intolerant at baseline. The hematologic failure patient lost his response because of an increase of  $\geq 30\%$  Ph+ compared to the lowest prior value, and the patient was discontinued due to 'unsatisfactory effect'. One of the IFN intolerant patients was also discontinued due to 'unsatisfactory effect' For the other patients, the cause of relapse/discontinuation was indicated as due to an increase of  $\geq 30\%$  Ph+ compared to the lowest prior value before the final assessment.

### Hematologic response rates

Table 62 provides the hematologic response rates for the ITT population (all disease groups), as well as for each disease group represented in this study.

**Table 62 Hematologic response rates-study 0110**

	<u>n (%)</u>	<u>95% CI</u>
<b>Overall (n=532)</b>		
Complete hematologic response	468(88.0%)	84.9-90.6
No response	54(10.2%)	
Not assessable	10(1.9%)	
<b>Hematologic Failures (n=152)</b>		
Complete hematologic response	126(82.9%)	76.0-88.5
No response	22(14.5%)	
Not assessable	4(2.6%)	
<b>Cytogenetic Failures (n=186)</b>		
Complete hematologic response	173(93.0%)	88.3-96.2
No response	12(6.5%)	
Not assessable	1 (0.5%)	
<b>INF Intolerant (n=194)</b>		
Complete hematologic response	169(87.1%)	81.6-91.5
No response	20(10.3%)	
Not assessable	5(2.6%)	

As previously noted for the cytogenetic response rates, with regard to hematologic responses, the hematologic failure group had complete responses that were slightly lower (82.9%, C195% 76.0-88.5) than those observed in the cytogenetic failure or IFN intolerant groups (93.0%, C195% 88.3-96.2; 87.1%, C195% 81.6-91.5, respectively).

### **Time to complete hematologic response**

By six months, there is no substantial difference in the disease groups as to those achieving a CHR, although the median time to achieving CHR for the hematologic failure group was slightly longer than the IFN intolerant or cytogenetic failure groups. (1.18 months Vs 0.72 months each for the latter groups. The duration of the CHR for all disease groups was also not markedly different, with an estimated probability of having a CHR lasting for 6 months or more over 80%.

### **Dose Escalations**

There were a total of 43 dose escalations reported (5 patients who escalated to 600 mg and then to 800 mg, 32 patients who were escalated directly to 800 mg, and 6 patients who were escalated to 600 mg). Of these, there were eight patients without an initial response at 400 mg who achieved a response after dose escalation. In addition, four patients with an initial response lost their response however, upon dose escalation, responded again. Fifteen patients never responded despite a dose increase.

### **Disease progression and survival**

The estimated probabilities of being free from progression to accelerated or blast crisis at 6 and 9 months were 94.4% and 91.0%, respectively. Time to disease progression was not different between all disease groups studied. Overall, the estimated probability of being free from progression at 6 and 9 months was 83.7% and 78.7%, respectively. At the cut-off date 19.2% (102/532 of patients) showed evidence of progression, but only 22 (4.1%) patients discontinued due to unsatisfactory effect (Table 7-1). Of these 102 patients, 3.9% (21/532) progressed to blast crisis, 3.4% (18/532) progressed to accelerated phase and 63 patients lost their response (11.8%) but were not considered to have progressed to unambiguous blast crisis or accelerated phase. Five of these progressions were found to have been present on Day 1, since these patients were actually in blast crisis (2 patients) or accelerated phase (3 patients) at the start of study and never responded.

The estimated 9-month survival rate from study entry for the overall population was 98.1 %

Of the cancer related symptoms whose severity (CTC Grade) was recorded at baseline there were only a few patients who achieved a Grade 3 for any symptoms. One (0.2%) each for arthralgia and abdominal discomfort and 3 (0.6%) for fatigue were reported). None achieved a Grade 4 level at any time during the study.

ECOG performance status at baseline was Grades 0 or 1 for 91.4% of patients (ITT population). Overall, no Grade 4 was recorded at any time during the study, and only 2 patients (0.4%) were recorded as Grade 3.

### **Fluorescent in-situ hybridization (FISH)**

Exploratory assessment of cytogenetic response using FISH methodology in addition to the standard karyotyping technique was performed in 302 patients. Among the 88

patients with a complete cytogenetic response who were assessed by the two techniques, 43 (48.9%) were also shown to be in complete response by FISH. The remaining 45 patients were assessed as partial [43 (48.9%)] or minor [2 (2.3%)] response.

## 8.6 FDA Results

Patients eligible for study 0110 had Ph+ chronic-phase disease with a documented failure of IFN or an IFN-containing therapy. This included:

**Hematologic Resistance** - defined as 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.

**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.

**Cytogenetic Resistance** - Bone marrow cytogenetics showing 65% Ph+ after one year of IFN-based therapy,

**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%.

**Interferon intolerance** - 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  $\geq 6$  months from the time of entry into the study.

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### 8.6.1 Patient characteristics

Characteristics of patients enrolled into study 0110 are listed in Table 63.

**Table 63 Patient characteristics per FDA-study 0110**

Characteristic	Value (N=532)
<b>CML Patient grouping</b>	
IFN Hematologic resistant/refractory	152
IFN Cytogenetic resistant/refractory	186
IFN intolerant	194
<b>Age</b>	
Median (range)	57.0 (18-90)
<b>Sex [N (%)]</b>	
Male	311 (58.5)
Female	221 (41.5)
<b>Race [N (%)]</b>	
Caucasian	463 (87.0)
Black	32 (6.0)
Other	37 (7.0)
<b>Performance status (ECOG) [N (%)]</b>	
0	314 (59.0)
1	172 (32.3)
2	18 (3.4)
Unknown	28 (5.3)
<b>Time from CML diagnosis [mo, (median range)]</b>	
IFN hematologic failure	32.9 (3-131)
IFN cytogenetic failure	32.7 (10-184)
IFN intolerant	29.6 (3-218)
<b>Duration of prior IFN ( 25 MIU/week [mo, (median range)]</b>	
IFN hematologic failure	12.1 (1-83)
IFN cytogenetic failure	22.0 (4-135)
IFN intolerant	7.1 (3-15)
<b>Interferon alone treatment</b>	
IFN hematologic failure	4 (2.6)
IFN cytogenetic failure	10 (5.4)
IFN intolerant	7 (3.6)
<b>Interferon plus</b>	
Hydroxyurea	484 (91.0)
Ara-C	273 (51.3)
Homoharringtonine	72 (13.5)
Other	21 (3.9)
<b>Chromosomal abnormalities [N (%)]</b>	
Ph positive	530 (99.5)
Ph pos + other chromosome abnormalities	87 (16.4)
Ph pos + missing data	25 (4.7)
<b>Extramedullary disease [N (%)]</b>	
Yes	129 (24.2)
No	403 (75.8)
<b>STI-571 Starting Dose [N (%)]</b>	
400 qd	524 (98.5)
600 qd	8 (1.5)

### 8.6.2 Cytogenetic response

Major cytogenetic response was the primary efficacy endpoint. Results of cytogenetic response analysis is summarized in Table 64. 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 64 indicates results for all relevant subgroups. Overall, the MCyR rate was 49.8% (265/532) in the FDA analysis. When compared to the sponsor's cytogenetic response analysis the FDA identified 2 additional patients with a MCyR (265 FDA versus 263 sponsor). The FDA identified fewer overall CCyR's than the sponsor although in the confirmed category the FDA number of CCyR's was greater than the sponsor's 84 or 89, depending on metaphase count for FDA and 78 for the sponsor. The probable explanation for the lowered overall CCyR rate was that the FDA scored patients who alternated between complete and partial response as partial responders rather than scoring based on best response. Despite the differences noted above, overall, the results of FDA and sponsor analysis of cytogenetic response were similar.

Overall 257/265 cytogenetic responders were censored for last date of response in the FDA analysis. The sponsor failed to provide comparable information. Estimates of median duration of cytogenetic response cannot be made since 98% of responders are censored.

**Table 64 Major cytogenetic response per FDA-study 0110**

	>=20 metaphases N=265/532 (49.8%)		Irrespective of # of metaphases N=265/532 (49.8%)	
	Confirmed*	Unconfirmed	Confirmed	Unconfirmed
Major CyR [N (%)]†	186 (70)	79 (30)	206 (78)	59 (22)
Complete	84 (32)	23 (9)	89 (34)	12 (4)
Partial	102 (38)	56 (21)	117 (44)	47 (18)
Patients censored for response duration	183/186 (98%)		203/206(98%)	

\*Confirmed - At least 2 marrows confirm a major cytogenetic response

Unconfirmed - Only a single marrow indicates a major cytogenetic response

† Denominator for (%) is 265

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 65 documents the course of two such patients. Both patients initially had a cytogenetic PR (>0 - 35% Ph+cells), followed by loss of PR, followed by CCyR (0% Ph+cells).

**Table 65 Variable cytogenetic response during therapy per FDA-study 0110**

Patient	Study day	CyR
4-1	88	PR
	176	NR
	271	CR
506-1	86	PR
	170	NR
	261	CR

NR= no response

The median number of days to the first cytogenetic analysis that demonstrated a MCyR is listed in Table 66.

**Table 66 Time to major cytogenetic response per FDA-study 0110**

	First MCyR Cytogenetics [median (d) (range)]
>=20 metaphases	89
Irrespective of # of metaphases	91

Because the interferon intolerant CML patient group differed from either the cytogenetic and/or hematologic resistant/refractory patient group in that they had not failed a prior therapy it is of interest to compare the MCyR rate in the two populations. These results are indicated in Table 67. The results were identical for the irrespective of # of metaphases and the 20 metaphase patient groups.

**Table 67 Major cytogenetic response by disease status per FDA**

	No. of Pts	MCyR's [n (%)]
IFN intolerant	194	113 (58.2)
Cytogenetic and/or hematologic resistant/refractory	338	152 (44.9)

### 8.6.3 Hematologic Response

A secondary efficacy endpoint is confirmed complete hematologic response (CHR). This result is indicated in Table 68.

Hematologic response data in the FDA analysis was comparable to the sponsor's confirmed hematologic response analysis 467 CHR's, FDA, 468 CHR's, sponsor. It is too early to determine response duration. In the FDA analysis 438 of the 467 responders (94%) are censored for response duration. The sponsor estimates that >80% will have a response duration of at least 6 months. Preliminary FDA response duration data is indicated in the table.

**Table 68 Complete hematologic response rate per FDA-study 0110**

Characteristic	N=532
Complete Hematologic Response (CHR) [N (%)]	467 (88.0)
Days to hematologic response- median (range)	22( )
Censored for response duration [N (%)]	438 (93.6)
Current Response durations [N (%)]	
>180d	293 (62.6)
>240d	161 (34.4)
>300d	4 (1.0)

CHR results for the interferon intolerant CML patient group and the cytogenetic and/or hematologic resistant/refractory patient group are summarized in Table 69. The results were comparable for the two patient groups.

**Table 69 Complete hematologic response by therapy group per FDA-study 0110**

	No. of Pts	CHR's [n (%)]
IFN intolerant	194	170 (87.6)
Cytogenetic and/or hematologic resistant/refractory	338	298 (88.2)

The definition for loss of CHR is not clear in the protocol. The FDA may be at fault for this. The sponsor suggested that loss of CHR required confirmation by two evaluations at least one month apart. The FDA (20 September 2000) suggested that no confirmation was required. Based on study results (Table 70), the sponsor's position may be more appropriate. Using a single determination for loss of CHR forty-four patients would have been declared non-responders on day 124 (median). These individuals continued on therapy, usually without an STI571 dose increase (39/44), and regained CHR (at least 2 consecutive determinations 28 days apart) and were still in response on day 253 (median).

**Table 70 Confirmed vs. unconfirmed loss of CHR per FDA-study 0110**

CHR's	N=468
CHR patients who lost and regained CHR	
Unconfirmed loss of CHR [n]	44
Confirmed loss of CHR [n]	4
Duration of first response [d] median (range)	65( )
Duration of second response [d] median (range)	Not determined
Time between responses [d] median (range)	19( )
STI571 Dose Increase [n]	5/44

#### 8.6.4 Cytogenetic and hematologic 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 71, 468 patients had a hematologic response and 265 had a major cytogenetic response. Two-hundred-fifty-two patients had both.

**Table 71 Combined hematologic and cytogenetic response per FDA -0110**

Efficacy response	No. of Pts
HR	468
MCyR	265
CHR + MCyR	252
CHR without MCyR	203
MCyR without CHR	13

#### 8.6.5 Symptoms

An important aspect of treatment is symptom relief. Table 72 describes common symptoms of CML patients and indicates their severity on four 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 evident on all follow-up evaluations.

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**Table 72 Patient symptoms per FDA -study 0110**

Visit	Symptom [N (%)]	0	1	2	3	No Data
1 d -7 to 0	Abdominal Discomfort (531)	492 (93)	23 (4)	3 (.6)	1	12
	Anorexia (531)	498 (93)	17 (3)	5 (1)	1	10
	Arthralgia (531)	460 (87)	39 (7)	14 (3)	4	14
	Bone Pain (531)	476 (89)	18 (3)	20 (4)	2	15
	Fatigue (531)	372 (70)	110 (21)	33 (6)	5	11
	Fever (531)	505 (95)	11 (2)	3 (.6)	1	11
	Night Sweats (531)	433 (82)	67 (13)	17 (3)	2	12
14 d 85	Abdominal Discomfort (516)	486 (94)	16 (3)	1	0	13
	Anorexia (516)	499 (97)	2 (.4)	2	0	13
	Arthralgia (516)	480 (93)	18 (3)	5	0	13
	Bone Pain (516)	496 (97)	5 (1)	3	0	12
	Fatigue (516)	453 (88)	43 (8)	7	0	13
	Fever (516)	503 (97)	1 (.2)	0	0	12
	Night Sweats (516)	483 (93)	19 (3)	1	0	13
20 w 25	Abdominal Discomfort (496)	476 (96)	12 (2)	0	0	8
	Anorexia (496)	483 (97)	5 (1)	0	0	8
	Arthralgia (496)	462 (93)	22 (4)	4	0	8
	Bone Pain (496)	476 (96)	12 (2)	0	0	8
	Fatigue (496)	452 (91)	29 (6)	6	1	8
	Fever (496)	484 (98)	3 (.6)	1	0	8
	Night Sweats (496)	472 (95)	14 (3)	2	0	8
22 or 24 w 37 or 49	Abdominal Discomfort (429)	405 (94)	7 (2)	1	1	13
	Anorexia (429)	413 (96)	1 (.2)	1	0	14
	Arthralgia (429)	404 (94)	8 (2)	2	1	14
	Bone Pain (429)	407 (95)	9 (2)	0	0	13
	Fatigue (429)	384 (90)	26 (6)	3	2	14
	Fever (429)	407 (95)	8 (2)	1	0	13
	Night Sweats (429)	398 (93)	16 (4)	2	0	13

**8.6.6 Performance status changes**

Performance status evaluation is shown in Table 73. For pretreatment performance status 1 or 2 patients a total of 115/189 individuals (61%) improved their performance status (at least 2 consecutive evaluations separated by at least 1 month) during treatment. Of equal importance only 31 of 498 patients (6%) had worsening performance status during treatment.

**Table 73 Performance status changes during therapy per FDA-study 0110**

Initial P.S.	No. of Pts N=536	Change in Performance Status N [(%)]			
		Improved	Stable	Worse	No data
0	316	--	284 (90)	26 (8)	6 (2)
1	174	101 (58)	65 (37)	5 (3)	3 (2)
2	18	14 (78)	3 (17)	0	1 (5)
Unknown	28				

## **9.0 Safety- All studies per sponsor and FDA**

The clinical safety datasets provided by the sponsor, for each of the phase II studies, were labelled A\_AEV. The laboratory safety datasets were labelled A\_LABH (hematology) and A\_LABB (biochemistry). The former table provided MEDDRA classifications, CTC grade, start and end dates, and other fields that were used, as appropriate. The laboratory datasets provide laboratory results as well as upper and lower normal values. The overall summary of safety came from the sponsor's integrated summary of safety. This summary was used because safety analysis of each study by the sponsor and FDA provided nearly identical results.

### **9.1 Relation to dose, duration of therapy**

Although a maximum tolerated dose was not formally established in chronic phase CML patients during the phase I trial (03 001), there was a higher frequency of Grade 3/4 study drug-related non-hematological AEs and of Grade 3/4 neutropenia and thrombocytopenia in patients treated at  $\geq 750$  mg daily, indicating that some patients did not tolerate doses of this magnitude when administered on a daily basis over many weeks.

In the 3 phase II studies, the initial doses were either 400 or 600 mg daily. Edema was the only AE, which was consistently reported at a higher frequency at the 600 mg dose. However, any interpretation is confounded by the fact that many patients were dose-escalated over time (from an initial dose of 400 to 600 or to 800 mg, or from 600 to 800 mg) and in all analyses AEs have been attributed to the initial dose received.

The onset of the most frequently reported Grade 1/2 AEs was generally during the first month of therapy whereas Grade 3/4 granulocytopenia and thrombocytopenia occurred on average after 2-4 weeks of therapy in advanced CML patients but only after 2 months in chronic phase patients.

An analysis has been carried out in the phase II studies to determine the effect of increasing the dose on the frequency and severity of adverse events. In this analysis, the frequencies of newly occurring/worsening adverse events were compared at the lower and higher dosages in patients who were dose-escalated. This analysis suggests that there is no consistent trend in the frequency and severity of AEs after dose escalation. The analysis is confounded by the longer duration of treatment of patients at the lower dosages and the fact that dose increases were invariably performed because of lack of efficacy.

### **9.2 Relation to disease-related factors**

The incidence of AEs was much higher in the advanced CML patients in studies 0102 and 0109 when compared to the chronic phase patients in 0110. This may be attributed to the much higher rate of disease-related complications in advanced phase patients though some of the differences may also be due to the fact that the majority of advanced disease patients were treated at the higher (600 mg) dose level.

### 9.3 Deaths

In the key safety population, a total of 158 patients died on study or within 28 days of discontinuation.

Only 6 of these deaths were reported from among the 616 chronic phase CML patients in 03-001 and 0110. One patient in 03-001 discontinued study medication and died 16 days later due to metastatic squamous cell carcinoma. In 0110, one patient died of a myocardial infarct whilst still receiving study drug. The other 4 patients died of complications related to progressive leukemia having stopped study medication within the previous 28 days.

In only two deaths, was a suspected relationship to study medication given by the investigator:

1. A 59-year-old male patient (505-0506) with CML in accelerated phase was enrolled in study 0109. At trial entry, he had been taking acetaminophen 3-3.5 grams daily for fever for several weeks and he continued this medication at high dosage. He also had a history of pneumocystis carinii pneumonia and herpes simplex meningitis. On Day 6 of therapy with STI571, the patient noted jaundice and was hospitalized on Day 7. STI571 and acetaminophen were discontinued. LFTs became grossly abnormal and the patient died on Day 12 due to liver failure, pulmonary hemorrhage and sepsis. Either a direct effect of STI571 or a possible drug interaction between STI571 and acetaminophen was suspected as leading to the death.
2. A 66-year-old man (012 001) with CML in myeloid blast crisis was enrolled in study 0102. On Day 4 of therapy, he developed bilateral pulmonary infiltrates for which he received antibiotics (Augmentin). Two days later, his urine output decreased and the serum creatinine increased to 190 pmol/L. Weight gain of approximately 5 kg was noted. There was an initial response to furosemide with a reduction in weight and in serum creatinine. STI571 was continued. On Day 12, oliguria was again present, together with bi-ventricular heart failure, pleural effusion and ascites. The patient experienced a sudden cardiovascular collapse and died within minutes.

An additional 4 patients in myeloid blast crisis in 0102 died with respiratory distress and signs of fluid overload. None of these deaths were attributed to the study medication by the investigator but some similarities to the above case warranted a closer examination of the circumstances. Two of these patients (007 0001 and 019 0001) had pleural effusions and pulmonary edema, with ascites in one case. However, there was also clear evidence of disease progression, which may well have been the major factor in causing death. The other 2 patients (002-0004 and 513-0002) developed respiratory difficulties and required intubation on Days 11 and 57, respectively, with death occurring 16 and 4 days later. A diagnosis of adult respiratory distress syndrome was made in both patients. In patient 002-0004, pulmonary edema on Day 11 was attributed to study medication. An autopsy was performed in patient 513-0002 but failed to establish the precise cause of death. An infectious process

appears most likely to explain the deaths in both patients, but a relationship to study medication cannot be completely excluded.

In 0109, two patients (003-0504 and 004-0521) died of infectious complications during the first 2 weeks of therapy while severely pancytopenic. Patient 003 0504 had Grade 3 ANCs at trial entry though the second patient had normal counts. In 0102, one patient (502-0007) became severely neutropenic during therapy and died of septic shock on Day 37. Peripheral blood blasts were present throughout indicating a lack of response. Although not reported as such by the investigators, STI571 may have contributed to these 3 deaths by lowering the neutrophil count as part of its anti-leukemic effect.

The causes of death in all other patients can be attributed to the underlying disease or to complications thereof.

#### **9.4 Serious adverse events**

A total of 454 SAEs were reported in the 1234 patients in the key safety population. The number of SAEs with a suspected relationship to study medication was 128. Only 27 possibly drug-related SAEs were reported in the chronic phase CML patients in studies 03-001 and 0110. The most commonly reported SAEs included nausea, vomiting, neutropenia, thrombocytopenia, febrile neutropenia, and skin rash (dermatitis), each in approximately 1% of patients. Thus, most SAEs were reported in acute phase patients and the majority were the result of complications related to progression of the underlying leukemia.

The following SAEs were selected for special consideration and are discussed individually.

##### **9.4.1 Rash**

Skin rash was reported as an SAE in 28 patients (2.3% of the key safety population). The rash was usually generalized and described as erythematous, maculopapular and frequently pruritic. There was an exfoliative component in 3 patients. The rash led to discontinuation in 7 patients, in all cases after a positive re-challenge, including 2 chronic phase CML patients. In some patients, the rash did not reappear when study medication was re-introduced after a temporary break, and in others the rash disappeared despite continued therapy.

##### **9.4.2 Liver**

Elevated liver function tests (LFTs) were reported as SAEs in 35 patients (2.8% of the key safety population). In almost all patients, the abnormalities comprised elevations of transaminases (SGOT and SGPT), either singly or in combination, with concomitant elevations of bilirubin in 11 of these 35 patients. Moderate (Grade 2) elevations of transaminases were the sole abnormality in 12 of these patients.

As described above, one patient in 0109 (505 0506) died due to liver failure which was suspected to be drug-related and 6 patients discontinued study medication because of liver AEs, including one patient with Budd Chiari syndrome that was suspected to be drug-related.

Of note, 3 of these 6 patients also had disease progression at the time of discontinuation. Only 2 chronic phase CML patients discontinued due to LFT elevations.

#### **9.4.3 Edema, fluid retention, weight gain**

This AE includes the following features: edema at various sites most commonly involving the soft tissues around the eyes and lower extremity edema, pleural effusions, and more rarely ascites, pericardial effusion, or generalized anasarca. Some patients reported significant weight gain, which was occasionally over 20 pounds. These symptoms usually developed during the first few weeks of therapy. When reported as an SAE, two or more of these features tended to be present at the same time. The complex of symptoms appeared to involve at least 2 possibly inter-related components: mainly fluid retention, but also an element of fluid redistribution since, in a few patients, pre-renal failure was also said to be present, possibly due to under-perfusion of the kidneys.

Some combination of these symptoms was reported as an SAE in 37 patients (3.0% of the key safety population). Fifteen of these patients had a history of ischemic heart disease or of prior episodes of pulmonary edema. With the exception of one fatality in 0102 (patient 012 0001), no patient discontinued study medication because of fluid-related symptoms. SAEs for fluid retention problems were reported in only 5 chronic phase CML patients.

As described, there was a fatal outcome in one patient (012 0001). This patient appeared to have an element of pre-renal failure, as mentioned above. Two additional patients require special mention. A patient (012 0506) with lymphoid blast crisis in 0109 developed severe headaches after 6 months of therapy at 600 mg daily. Cerebral edema was visualized by CT scan, without evidence of CNS leukemia. A second accelerated phase patient in 0109 developed bilateral macular edema shortly after eye surgery. Both episodes were suspected to be related to the study medication by the investigators.

In addition, 5 patients developed pericardial effusions during the study, 3 of which were believed to be drug related.

#### **9.4.4 Renal toxicity**

Renal function abnormalities (predominantly elevated creatinine levels) were reported as SAEs in 20 patients (1.6% of the key safety population). One episode was a

component of the events leading to death from fluid overload problems, as described above (patient 012 0001). Most of the remaining events occurred in terminally ill patients and in the setting of progressive leukemia. At least two episodes seem to have been triggered by severe vomiting. Two of these 17 patients (0502 0503 in study 0109; 02/14 in study 03 001) manifested tumor lysis syndrome, which was associated in one (patient 02/14) with therapy with concomitant high-dose hydroxyurea.

#### **9.4.5 Gastrointestinal hemorrhage**

GI hemorrhage was reported as an SAE in 26 patients (2.1% of the key safety population). Only 3 chronic phase patients reported GI bleeding, including one episode of bleeding due to diverticular disease and one associated with disease progression, both in study 0110.

However, one additional chronic phase patient (01/04) in the phase I study had a GI bleed just 48 hours after stopping study medication at a dose of 85 mg daily.

All other patients had acute phase disease and, significantly, Grade 3/4 thrombocytopenia was present in 13. Ulcers (esophageal, gastric or duodenal) were visualized at gastroscopy in 7 patients and Mallory Weiss tears related to severe vomiting were suspected or demonstrated to be the cause of bleeding in 4 others. A single patient discontinued due to GI bleeding, though only because he needed to start therapy with a proton pump blocker, which was prohibited by the protocol at the time the event took place.

In addition, one patient (01/45) with myeloid blast crisis in the phase I study (03 001) died from complications relating to a GI hemorrhage in the weeks following data cut-off.

#### **9.4.6 Subdural hematoma/cerebral hemorrhage**

CNS bleeding was reported as an SAE in 32 patients (2.6% of the key safety population). Subdural hematomas were present in 12 patients and intracranial bleeding in 20 patients. Grade 3/4 thrombocytopenia was documented at the time of bleeding in 22 patients. A subdural hematoma in an accelerated phase patient (506 0525) in 0109 was attributed to longstanding Factor V deficiency.

There were two CNS bleeding episodes in chronic phase patients in study 0110. A 70-year-old male patient (503 0125) with a normal platelet count (150x10<sup>9</sup>/L) experienced a cerebral hemorrhage. There was a history of coronary artery disease and hypercholesterolemia. A 68 year-old male (509 0008), also with a normal platelet count, developed intracerebral bleeding on Day 18. He was receiving warfarin for thrombosis prophylaxis and the coagulation parameters were significantly prolonged. A drug interaction was suspected, due either to competition at the level of the liver cytochromes or to displacement effects on plasma proteins, or to some combination of these effects.

Study-drug-related SAEs, grouped by preferred terms, are presented in Tables 74-76 for studies 0102, 0109 and 0110, respectively.

**Table 74 Study-drug related AE's- Study 0102**

Event N=260	Severity a		SAE b	Discontinuation b	Dose reduction or interruption b
	All grades	Grade 3/4			
Edemas	133(51.2)	8(3.1)	4(1.5)	1(0.4)	5(1.9)
Fluid retention	18(6.9)	6(2.3)	7(2.7)	0	2(0.8)
Skin rash	55(21.2)	9(3.5)	6(2.3)	3(1.2)	12(4.6)
Hemorrhage	24(3.2)	6(2.3)	46(17.7)	7(2.7)	12(4.6)
Cerebral/subdural	0	0	11 (4.2)	1(0.4)	0
GI tract	5(1.9)	4(1.5)	6(2.3)	2(0.8)	6(2.3)
Renal failure	3(1.2)	1 (0.4)	8(3.1)	3(1.2)	0
Liver failure	13(5)	7(2.7)	9(3.5)	1(0.4)	15(5.8)
Joint pain	18(6.9)	2(0.8)	3(1.2)	0	1 (0.4)
Myalgia	12(4.6)	0	0	0	0
Cramps	61(23.5)	1(0.4)	0	0	0

a Study-drug-related events; b all events

**Table 75 Study-drug related AE's - Study 0109**

Event N=293	Severity a		SAE b	Discontinuation b	Dose reduction or interruption b
	All grades	Grade 3/4			
Edemas	172(58.7)	6(2)	5(11.7)	0	12(4.1)
Fluid retention	21(7.2)	4(11.4)	9(3.1)	0	3(1)
Skin rash	67(22.9)	7(2.4)	7(2.4)	2(0.7)	11(3.8)
Hemorrhage	29(9.9)	4(1.4)	25(8.5)	4(1.4)	7(2.4)
Cerebral/subdural	1 (0.3)	0	3(1)	1(0.3)	0
GI tract	3(1)	2(0.7)	3(1)	2(0.7)	2(0.7)
Renal failure	3(1)	1 (0.3)	7(2.4)	1(0.3)	0
Liver failure	13(4.4)	8(2.7)	10(3.4)	1(0.3)	13(4.4)
Joint pain	33(11.3)	7(2.4)	2(0.7)	0	4(1.4)
Myalgia	29(9.9)	3(1)	1 (0.3)	0	2(0.7)
Cramps	77(26.3)	0	0	0	0

a Study-drug-related events b all events

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**Table 76 Study-drug related AE's - Study 0110**

Event N=532 (0/6)	Severity a		SAE b	Disconti uation b	Dose reduction or interruption b
	All grades	Grade 3/4			
Edemas	248(46.6)	6(1.1)	2(0.4)	0	10(1.9)
Fluid retention	69(13)	10(1.9)	3(0.6)	0	1 (0.2)
Skin rash	137(25.8)	17(3.2)	6(1.1)	2(0.4)	28(5.3)
Hemorrhage	12(2.3)	0	4(0.8)	0	3(0.6)
Cerebral/subdural	1 (0.2)	0	2(0.4)	0	0
GI tract	0	0	0	0	0
Renal failure	2(0.4)	0	2(0.4)	0	1 (0.2)
Liver failure	9(1.7)	6(1.1)	7(11.5)	2(0.4)	10(1.9)
Joint pain	67(12.6)	2(0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Myalgia	75(14.1)	1 (0.2)	0	0	2(0.4)
Cramps	238(38.7)	4(0.8)	0	0	1 (0.2)

a Study-drug-related events; b all events

#### Other significant adverse events

One patient in 0109 (007 0501) developed pancreatitis, which according to the investigator was suspected to have been related to study drug. However, once the episode had resolved, study drug was resumed at the same dose without recurrence of symptoms making an association unlikely.

#### AEs leading to dose reduction/interruption

The most common AEs leading to dose reduction/interruption in both chronic and acute phase patients (in approximately 10%) were granulocytopenia and thrombocytopenia. Nausea, vomiting, diarrhea, rash, edemas, liver function test abnormalities, and musculoskeletal complaints were other reasons for dose reduction/interruption, occurring in 1-5% of patients.

#### 9.4.7 Summary of adverse event findings

The most commonly reported AE with a suspected relationship to STI571 across all studies has consistently been mild to moderate nausea, sometimes accompanied by vomiting, dyspepsia and/or upper abdominal pain. GI symptoms were noted in 40 patients in study 0102, 27 patients in study 0109 and and 8 patients in study 0110. These symptoms likely relate to a direct irritant effect of STI571 on the upper GI tract mucosa. When pharmacokinetic data became available indicating that food had little effect on absorption, STI571 was administered with food (as opposed to 2 hours following breakfast) for the last months of these studies. Feedback from investigators suggests that this has considerably improved the GI tolerability of STI571 though no formal documentation is available as yet to support this.

Other common AEs reported included the appearance of edema at various sites, most frequently in the periorbital region, and musculoskeletal symptoms including muscle cramps, myalgia and arthralgia. Diarrhea, maculopapular skin rash and headache were the next most frequently reported AEs. The edema collections have led in a minority

of patients to substantial increases in weight. No patient discontinued study medication because of edema.

AEs have generally been mild to moderate (Grade 1/2) in severity with Grade 3/4 episodes reported in <5% of patients. Other than a slight increase in the frequency of Grade 1/2 edemas (periorbital and lower limb), there was no evidence of an altered safety profile in patients  $\geq 65$  years. There was also no relationship to sex, except for a slight increase in Grade 1/2 periorbital edemas, headaches and fatigue in women. Discontinuation due to study-drug related AEs has been uncommon occurring in 1-5% of patients with the lowest incidence in chronic phase patients. This figure is probably an over-estimate because of the inclusion of patients who actually discontinued due to disease progression but who happened to have a drug-related AE at the same time.

SAEs were reported in a large number of patients though less than one third had a suspected relationship to STI571. Apart from myelosuppression, which was an expected pharmacological effect of the compound on the leukemic bone marrow, the following SAEs were identified as worthy of special consideration:

Rash - variously described as generalized, erythematous, maculopapular or pruritic, and very occasionally with an exfoliative component. Although quite severe in a minority of patients, rashes led to permanent discontinuation in only 7 patients.

Liver toxicity - manifesting most commonly as elevations in transaminase levels though sometimes accompanied by elevations in bilirubin and alkaline phosphatase.

Fluid retention/redistribution, edema and/or renal toxicity - potentially the most problematic AE related to STI571 therapy, and consisting in the more severe cases of generalized fluid retention with considerable weight gain and the appearance of pleural effusions and more rarely of pericardial effusions (in 5 patients) and ascites. In some patients with a prior history of ischemic heart disease, congestive cardiac failure has been precipitated. In a minority of patients, the redistribution of fluid may have led to pre-renal failure. There was no evidence of direct nephrotoxic effects of STI571. Fluid retention appeared to correlate with tumor burden, i.e. it was more likely to be noted in patients enrolled in study 0102 and 0109 than in patients enrolled in 0110. Thus 65 of 260 patients (25%) in study 0102 had edema of greater than or equal to grade 2 in severity. Corresponding figures for study 109 and 0110 were 53 of 235 (23%) and 46 of 532 (9%), respectively.

GI tract hemorrhage - though often occurring in the setting of profound thrombocytopenia, it is likely that at least some of these cases were related to the local irritant effects of STI571.

CNS hemorrhage - episodes of cerebral bleeding were generally associated with profound thrombocytopenia and the incidence in these studies seemed no higher than might be expected in this patient population.

Irrespective of any suspected relationship to study medication, each of these SAEs was reported in <3% of patients.

There were 2 deaths with a suspected relationship to study medication. An accelerated phase CML patient who was taking high doses of acetaminophen died due to hepatic failure, possibly due to a drug-drug interaction. A myeloid blast crisis patient died due to fluid retention, followed by congestive cardiac and renal failure.

In an additional 2 patients, complications related to fluid retention/redistribution might have contributed to the death though none were assessed as suspected by the investigator. Three patients died of infectious or bleeding complications whilst severely pancytopenic.

#### **9.4.8 Serum chemistry**

Grade 3/4 elevations in LFT's were recorded more frequently in acute than in chronic phase patients. The incidence of Grade 3 abnormalities in parameters of liver function in acute phase patients in 0102 and 0109 ranged from 2-5% whereas in chronic phase patients the incidence was (often considerably) less than 2.5% of patients. Grade 4 LFT changes were reported in <1% of acute phase patients; no chronic phase patient experienced Grade 4 elevations. In the acute phase patients, deranged liver function was frequently either a pre-terminal event in the setting of generalized organ failure, or was due to presumed or (occasionally) documented leukemic cell infiltration of the liver.

The time to onset of Grade 3 transaminases was highly variable between patients with medians of 129 and 155 days in 0110 and 0109, with the abnormalities persisting for an average of 2-4 weeks.

Grade 3 elevations in serum creatinine were uncommon and were reported in 3 patients each in 0102 and 0109. All 6 patients were critically ill or had pre-existing renal problems at study entry. No Grade 4 values were reported in any study. In only a single chronic phase patient (504 001 in 0 110) was an SAE reported due to Grade 2 elevation of creatinine and Grade 3 hyperkalemia. This resolved rapidly with hospital treatment and ST1571 was resumed at a reduced dose and had not recurred after 3 additional months of therapy.

Grade 3 hyponatremia and hypophosphatemia were each recorded in about 10% of chronic and acute phase patients and hypokalemia in 7%, without an obvious explanation.

#### **9.4.9 Hematology**

The numbers of patients in each study with newly occurring or worsening Grade 3/4 hematology values whilst receiving study medication are summarized in Tables 77 to 80.

In the phase I study (03 001), Grade 3/4 neutropenia and thrombocytopenia occurred in 15/22 patients treated at doses  $\geq$ 750 mg.

In chronic phase patients in 0110 (treated at 400 mg daily), Grade 3 neutropenia and thrombocytopenia were reported in 25% and 16% of patients, respectively, but Grade 4 events occurred in only 8% and 0.5 %. Peripheral blood cytopenias were considerably more frequent in the acute phase patients in 0102 and 0109 with Grade 3 neutropenia and thrombocytopenia in approximately 15% and 25%, and Grade 4 values in 50 % and 30%, respectively.

The median time to the onset of Grade 3/4 neutropenia and thrombocytopenia was shorter in 0102 in comparison to 0109 and 0110 - 2 weeks Vs 5-8 weeks - with the longest times consistently seen in the chronic phase patients. The median duration of Grade 3/4 neutropenia and thrombocytopenia was 2-4 weeks in all studies. Grade 3 lymphopenia was recorded in approximate 25% of chronic phase patients but in 50% of acute phase patients.

There were 2 episodes of neutropenic sepsis in chronic phase patients during the phase I study and one episode of bleeding, each occurring at doses of 800 and 1000 mg, respectively. In the chronic phase patients in 0110, there were also 2 episodes of febrile neutropenia requiring hospitalization and treatment with intravenous antibiotics but no episodes of thrombocytopenic hemorrhage.

As expected, infection and bleeding were much more frequent in the acute phase patients in 0102 and 0109. Serious infectious episodes occurred in 13% and 19% of patients in 0109 and 0102, respectively, and serious bleeding in 6% and 18%.

**Table 77 CTC Grade 3/4 hematology abnormalities - Study 03 001**

Hematology parameter	CTC	Adult	Adult	All
	Grade	chronic	acute	pediatric
	3/4	N=84 (%)	N=59 (%)	N=6(%)
Hemoglobin	3	7(8.3)	23(39.0)	0
	4	0	5(8.5)	2(33.3)
WBC	3	16(19.0)	18(30.5)	2(33.3)
	4	2(2.4)	14(23.7)	3(50.0)
ANC	3	20(23.8)	15(25.4)	0
	4	4(4.8)	18(30.5)	3(50.0)
Platelets	3	16(19.0)	18(30.5)	1 (16.7)
	4	2(2.4)	20(33.9)	3(50.0)
Absolute lymphocytes	3	30(35.7)	39(66.1)	4(66.7)

WBC = white blood cell, ANC = absolute neutrophil count.

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**Table 78 CTC Grade 3/4 hematology abnormalities - Study 0102**

Hematology parameter	CTC grade	400 mg N=37 (%)	600 mg N=223 (%)	All doses N=260 (%)
Hemoglobin	3	16(43.2)	89(39.9)	104(40.0)
	4	6(16.2)	20(9)	26(10.0)
WBC	3	9(24.3)	78(34.9)	87(33.5)
	4	10(27.0)	38(17.0)	48(18.5)
ANC	3	5(13.5)	37(16.6)	42(16.1)
	4	19(51.4)	101 (45.3)	120(46.1)
Platelets	3	10(27.0)	61 (27.3)	71 (27.3)
	4	12(32.4)	69(30.9)	81 (31.2)
Absolute lymphocytes	3	16(43.2)	127(56.9)	143(55.0)
	4	0	0	0

WBC= white blood cell, ANC= absolute neutrophil count

**Table 79 CTC Grade 3/4 hematology abnormalities - Study 0109**

Disease group:	CML AP (primary group)			ALL	AML	LBC
Initial dose (mg/day):	400 mg	600 mg	all doses	N=48(%)	N=2(%)	N=8(%)
	N=77(%)	N=158(%)	N=235(%)			
Hematology parameter:						
Hemoglobin						
G3	26(33.8)	48(30.4)	74(31.5)	17(35.4)	2(100)	0
G4	6(7.8)	6(3.8)	12(5.1)	3(6.3)	0	1(12.5)
WBC						
G3	20(26.0)	55(34.8)	75(31.9)	14(29.2)	1(50.0)	1 (12.5)
G4	14(18.2)	20(12.7)	34(14.5)	20(41.7)	1 (50.0)	3(37.5)
ANC						
G3	16(20.8)	40(25.3)	56(23.8)	7(14.6)	0	0
G4	26(33.8)	53(33.5)	79(33.6)	23(47.8)	2(100)	4(50-0)
Platelets						
G3	24(31.2)	47(29.7)	71(30.2)	11 (22.9)	0	1(12.5)
G4	10(13.0)	19(12.0)	29(12.3)	14(29.2)	1(50.0)	1(12.5)
Absolute lymphocytes						
G3	41 (53.2)	83(52.5)	124(52.8)	25(52.1)	1 (50.0)	5(62.5)

WBC= white blood cell, ANC= absolute neutrophil count.

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ON ORIGINAL**

**Table 80 CTC Grade 3/4 hematology abnormalities - Study 0110**

400 mg/d Hematology parameter	CTC Grade	Hematologic	Cytogenetic	IFN Intolerant N=194 (%)	Overall N=532 (%)
		Failure N=152 (%)	Failure N=186 (%)		
Hemoglobin	3	4(2.6)	9(4.8)	7(3.6)	20(3.8)
	4	3(2)	1 (0.5)	1 (0.5)	5(0.9)
WBC	3	22(14.5)	48(25.8)	39(20.1)	109(20.5)
	4	1 (0.7)	5(2.7)	3(1.5)	9(1.7)
ANC	3	26(17.1)	60(32.3)	44(22.7)	130(24.4)
	4	11 (7.2)	16(8.6)	15(7.7)	42(7.9)
Platelets	3	23(15.1)	41 (22)	22(11.3)	86(16.2)
	4	0	1 (0.5)	1 (0.5)	2(0.4)
Absolute lymphocytes	3	36(23.7)	57(30.6)	55(28.4)	148(27.5)
	4	0	0	0	0

#### 9.4.10 Laboratory data summary

Grade 3/4 elevations of LFT's were reported in up to 2.5% and 5% of chronic and acute phase patients, respectively. Time of onset was highly variable between patients with a median of over 100 days and a duration of 2-4 weeks.

Grade 3 elevations of serum creatinine were rare, and tended to occur only in terminally ill patients. Grade 3 electrolyte disturbances - hypokalemia, hyponatremia, and hypophosphatemia - were reported in 5-10% of patients.

In chronic phase patients, Grade 3 neutropenia and thrombocytopenia were relatively common (in 25% and 16% of patients, respectively) whereas Grade 4 events were infrequent (8% and 0.5%, respectively). The median time to onset was approximately 2 weeks in myeloid blast crisis patients but 5-8 weeks in accelerated and chronic phase patients. The median duration of Grade 3/4 cytopenias was 2-4 weeks across all studies. Febrile neutropenia and bleeding as a consequence of cytopenias were uncommon in chronic phase patients. In acute phase patients, Grade 4 neutropenia and thrombocytopenia were more frequent (50% and 30% of patients respectively) and as a consequence there was a much higher incidence of infection and bleeding, though no more than expected in a patient population with advanced leukemia.

#### 9.4.11 Cardiac Rhythm Disorders

Repeat ECGs were carried out only in studies 03 001 and 0102. In addition to an ECG at baseline, an ECG was repeated after 8 weeks treatment in 03 001, and after one week in 0102. ECG's were interpreted locally. In all studies, ECGs were carried out as clinically indicated and relevant findings reported as AEs, if appropriate.

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The numbers of patients in whom cardiac rhythm disorders were reported as SAEs are summarized by study in Table 81.

**Table 81 ECG and serious cardiac rhythm disorders**

Study	Patients	New/worsening Abnormalities	Serious cardiac rhythm AEs	
			All	Drug-related
03001	Adult chronic	2	0	0
	Adult acute	6	1	0
	Pediatric	0	0	0
0102	Blast crisis CML	14	5	2
0109	Accelerated phase CML	nd	2	0
110	Chronic phase CML	nd	3	0

nd=not done

Patients with serious cardiac rhythm disorders are itemized in Table 82. There were 11 episodes in 10 patients and all events were either pre-existing or were secondary to other AEs. Both cases in which the investigator noted a suspected drug-relationship (study 0102: patients 008 0003, 503 0013) involved tachycardia with onset during a febrile episode.

**Table 82 Patients with serious cardiac rhythm AE's**

Study patient (sex,age)	Dosage (mg/d)	Day of onset	Event	Causality NS/S	Comments
03 001 03/16 (M,62)	300	6	Nodal arrhythmia	NS	coronary artery disease, atrial fibrillation
0102 005 0010 (M,56)	600	64	Tachycardia	NS	associated with hypertension
007 0006 (M,73) also	600	20	Tachycardia	NS	pulmonary edema
008 0003 (M,41)	600	235	Tachycardia	S	accompanying septicemia
502 0025 (M,65)	600	28	Cardiac arrest	NS	coronary artery disease, hypertension, MI
503 0013 (F,52)	600	20	Supraventricular tachycardia	S	present at baseline neutropenic fever also as SAE.
0109 503 0537 (F,50)	600	9	Tachycardia	NS	pneumonia
503 0558 (F,76)	600	55	Atrial fib	NS	heart failure
0110 003 0012 (F,55)	400	5	Tachycardia	NS	present at baseline
		122	Nodal arryth	NS	hyperthyroid
503 0008 (M,39)	400	32	Atrial fib	NS	present at baseline

NS= not suspected; S=suspected

## 10.0 Financial disclosure

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

- No principal or sub-investigators were full or part-time Novartis employees.
- [redacted] study 0109 declared that he had received payment of other sorts. Consultant for Novartis and member of International Advisory Board.
- [redacted] study 0102 ([redacted]) and study 0110 (center 19) declared that she had a significant equity interest in the sponsor.
- Despite best efforts by the sponsor several investigators did not return forms. Any bias that is introduced from this lack of information is minimized by independent data monitoring by Novartis and by the multiple investigators participating in these studies.

### Conclusion

Based on the above it does not seem likely that individuals who have not provided financial disclosure information could have significantly biased study results.

## 11.0 Study synopses

### 11.1 Study 0102

**Title of study:** A phase II open-label study to determine the safety and anti-leukemic effects of ST1571 in patients with Philadelphia chromosome-positive chronic myeloid leukemia in myeloid blast crisis.

**Study center(s):** France (3), Germany (5), Italy (5), UK (3), Switzerland (2) and the USA (14)

**Study period:** First patient enrolled: 26 Jul 1999 Last patient completed: 02 Oct 2000 (cut-off date) which was 3 months after recruitment of the last patient.

**Primary objective:** Rate of hematologic response (confirmed after 4 weeks). The main target population was Philadelphia (Ph) chromosome-positive myeloid blast crisis patients not previously treated with agents other than interferon and hydroxyurea.

**Secondary objectives:** Duration of hematologic response, overall survival, cytogenetic response, safety, improvement in disease-related symptoms and ECOG performance status. The pharmacokinetic profile of ST1571 was also studied in a sub-group of patients.

**Investigational drug:** ST1571 was provided in capsule form, initially in 25mg, 50 mg, 100 mg strengths and after implementation of amendment 2, in 100 mg strength only. Initial dose was either 400mg/d (pre-amendment 2), or 600 mg/d (amendment 2). Dosage increase 800mg/d (400 mg bid) was permitted in all patients (amendment 2) for improved therapeutic effect.

**Duration of treatment:** The study was open-ended with patients able to remain on treatment for as long as they were alive and able to derive benefit

**Number of patients:** 260 patients were recruited, of whom 165 had not previously received antineoplastic treatment for advanced CML (accelerated phase or blast crisis).

**Statistical methods:** Confirmed hematologic response rate was evaluated using Fleming's single-stage, single-arm test procedure ( $H_0: p \leq 15\%$  and  $H_1: p > 30\%$ ). With  $\alpha = 2.5\%$  (one-sided) and power = 90%, the required number of responders were 19/79 in the untreated patient group for the planned 100 patients. This number was revised to 35/165 due to the increased recruitment in the study. All 95% confidence intervals were calculated using Pearson-Clopper limits. Time to event variables were evaluated using Kaplan-Meier method.

**Efficacy:** As shown by the primary efficacy outcome, the target rate of at least 35/165 overall confirmed hematological response in untreated patients with a lower 95% CI limit above 15% was achieved. Hematologic response rates were comparable in sponsor and FDA analyses.

Disease subgroup	Untreated N=165	Treated N=95	TOTAL N=260
<b>Hematologic response:</b>			
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)
No response/progression/death	96(58.1)	66(69.5)	162(62.3)
Not assessable	19(11.5)	11(11.6)	30(11.5)

The median time to response was approximately one month. Median response duration was 6.6 months in the sponsor's analysis and 5.6 months in the FDA analysis. Response rate was higher in untreated patients than in treated patients (30.3% Vs 18.9%) and in the 600 mg/d group than in the 400 mg/d group (28.7% Vs 10.8%).

Major cytogenetic responses were recorded in 14% of patients. It is too early to estimate the median duration of response

**Safety:** 82 (31.5%) patients died while on treatment or within 28 days of their last dose of ST1571. Infections and hemorrhages were frequent and accounted for most deaths not considered as disease progression. One death was suspected to be drug-related. This patient developed ascites and pleural effusion that progressed to renal and cardiac failure.

AEs, which were frequent but with little consequence for the ability of patients to remain on treatment included gastrointestinal events (nausea, vomiting, diarrhea, abdominal pain) skin rash, muscle cramps, myalgia, and arthralgia. Edema occurred in 63% of patients and was of grade 3/4 severity in 13 (5%).

65% of patients experienced serious AEs. AEs were the primary reason for discontinuation in 8% of patients. Drug interruption or dosage adjustment occurred in

43% of patients because of AEs. Fluid redistribution abnormalities (pleural effusion, pulmonary edema, ascites, congestive heart failure) and edema occurred in 19 (7.3%) patients. These contributed to the deaths of 8 patients. In 6/19 patients a drug-relationship appears possible.

Newly occurring or worsening severe (grade 3-4) neutropenia (62%), thrombocytopenia (58%), lymphopenia (55%) and anemia (50%) were also frequent. Drug-induced reduction in leukocytosis and blasts did not necessarily lead to recovery of normal hematopoiesis.

Overdose (1200mg/d for 8 days) in one patient resulted in grade 2 hepatic cytolysis and grade 3 cholestasis reversible on interruption of treatment and no repetition on resumption of ST1571 (400mg/d). Mild liver toxicity may have occurred in 4 patients on dosages on 600-800mg/d. There was no evidence for drug-induced renal toxicity.

Conclusions: Hematologic response was noted in 26% of patients and occurred generally within a month. Response was more frequent in patients previously-untreated for advanced CML than in those previously treated and at a dosage of 600mg/d than 400mg/d. A major cytogenetic response occurred in 14% of patients. Medullary aplasia could be prolonged. Liver toxicity was associated with drug overdose in one patient although it also occurred in patients on doses of 600-800 mg/d. Complications of fluid overload or redistribution, was an uncommon but potentially serious drug effect.

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## 11.2 Study 0109

**Title of study:** A Phase II study to determine the safety and anti-leukemic effects of STI571 in adult patients with Philadelphia chromosome positive (Ph+) leukemia including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), lymphoid blast crisis (LBC) chronic myeloid leukemia (CML) and accelerated phase (AP) chronic myeloid leukemia.

**Study center(s):** 18 centers in 6 countries: France (2), Germany (4), Italy (3), UK (2), Switzerland (1) and USA (6)

**Study period:** First CML AP patient recruited: 09-Aug-99. Last CML AP patient recruited: 22-Feb-00. First acute leukemia patient recruited: 13-Sep-99. Last acute leukemia patient recruited: 12-May-00. Cut-off date: 09-Oct-00

**Objectives:** The primary efficacy outcome was the overall rate of confirmed hematologic response in CML AP patients. Secondary efficacy variables included cytogenetic response, overall survival, ECOG performance status and cancer related symptom improvement, safety and pharmacokinetics.

**Methodology:** Patients received STI571 400mg or 600mg orally once a day. Dose escalation was permitted, to a maximum of 400mg twice a day (800mg). Patients continued STI571 indefinitely if they had benefit and tolerable side effects.

**Number of patients:** 293 enrolled patients in total: 235 with CML AP, 48 with relapsed/refractory ALL, 2 with relapsed/refractory AML, 8 with relapsed/refractory CML in LBC (recruitment of this disease group was stopped after protocol amendment 2.

**Inclusion criteria:** Consenting adult, male and female patients, aged 18 years with histologically confirmed Ph+ leukemia of either CML AP, or relapsed/refractory ALL or AML, or CML in LBC, and specified values of clinical laboratory parameters (transaminases, creatinine) and ECOG performance status score of <3.

**Statistical methods:** The study was designed to evaluate the confirmed hematologic response rate using Fleming's single-stage, single-arm test procedure. ( $H_0: p = 30\%$  and  $H_1: p = 50\%$ ). With  $\alpha = 2.5\%$  (one-sided) and  $\text{power} = 90\%$ , the planned required number of responders was 29/68 in the CML AP patient group. This number was revised to 85/235 due to the increased recruitment in the study. All 95% confidence intervals (CI) were calculated using Pearson-Clopper limits. Time to event variables were evaluated using the Kaplan-Meier method. Safety variables were analyzed by frequency counts of adverse events, and shift table analysis of newly occurring grade 3 or 4 laboratory abnormalities.

**Results: Demographics:** 235 CML AP patients; 118 males, 117 females; 210 caucasian, 10 black, 15 other race; mean age 55.8y, range 22-86y. 48 ALL, 2 AML, 8 CML in LBC patients.

Efficacy in CML AP: The confirmed, calculated hematologic response rates were:

Population:	Intent to treat		
	400 mg N=77	600 mg N=158	all doses N=235
Hematologic response			
n(%)	48 (62.3)	100 (63.3)	148 (63.0)
95% CI	50.6-73.1	55.3-70.8	56.5-69.2
Complete remission	21 (27.3)	44 (27.8)	65 (27.7)
No evidence leukemia	7 (9.1)	20 (12.7)	27 (11.5)
Return chronic phase	20 (26.0)	36 (22.8)	56 (23.8)

The median time to overall hematologic response was 1 month, range 0.9 to 9.3 months. It is too early to estimate the median duration of response.

Cytogenetic response rates in the ITT population were:

Initial dose group:	400 mg N=77	600 mg N=158	all doses N=235
Major response (complete+partial)			
n (%)	12 (15.6)	38 (24.1)	50 (21.3)
95% CI	8.3-25.6	17.6-31.5	16.2-27.1
complete	7 (9.1)	27 (17.1)	34 (14.5)
partial	5 (6.5)	11 (7.0)	16 (6.8)
Time to major cytogenetic response (months)			
Median (range)	2.46 (0.8-11.7)	2.83 (1.0-8.5)	2.83 (0.8-11.7)

It is too early to estimate overall survival rate.

**Safety in CML AP:** All but one of the patients experienced AEs, mostly grade 1/2 severity. Only 2% discontinued for AEs possibly related to STI571. 35 (15%) patients died within 28 days of their last dose of STI571. One death was considered possibly drug-related: liver failure in an AP patient who received 7 days STI571 therapy (600mg/day), before discontinuing due to hepatotoxicity. This patient was also taking paracetamol, another known hepatotoxic drug.

Frequently reported AEs included gastrointestinal (GI) events (93% of patients, 16% grade 3-4), principally nausea (68%), vomiting (54%), diarrhea (49%), dyspepsia (19%), abdominal pain (15%) and constipation (13%). Edema, most often periorbital, was noted in 66% of patients (62% grade 1-2). Skin rash (39% of patients, 35% grade 1-2), muscle cramps (34%), myalgia (20%), and arthralgia (26%) were also frequent but only rarely severe (0.4%, 2% and 5%, respectively). The incidence of edema was 52% in patients who initiated treatment at 400mg/day compared with 73% at 600mg/day. Two affected patients required interruption of STI571 treatment. For 6 (3%) patients, skin rash was serious, recurred upon re-challenge in 2 patients and led to permanent study withdrawal in one case of maculopapular rash. In one other patient, the skin rash was not reported as serious, but led to study discontinuation after a positive rechallenge. Renal failure was

reported in 11 patients (5%). However, in all but one case this event occurred in the context of terminally ill patients with progressive leukemia.

Grade 3 elevations in transaminases occurred in 3% of patients usually after several months of therapy with a median duration of 11 days (range 5-35 days). 6% experienced grade 3 or 4 increase in alkaline phosphatase and 2% had grade 3 hyperbilirubinemia. Generally, grade 3 or 4 elevations in LFTs have been reversible and manageable with drug interruption or dose reduction. Liver toxicity was reported as serious in 10 patients (4%), considered drug related in 6, led to study withdrawal in one case and was fatal in one other.

Hematologic toxicity was frequent. Grade 3 or 4 neutropenia (57%), thrombocytopenia (44%) and anemia (37%) were noted. Median duration of grade 3 or 4 ANC was 21 days (range 1-317 days). 26% of the patients had their dose interrupted or reduced at the time of grade 3 or 4 neutropenia. Febrile neutropenia was reported in 5% of patients. Serious infectious episodes were reported in 13%, and were reported as the principal cause of death in 3%.

Serious bleeding episodes were reported in 14 patients (6%). Six were GI hemorrhages, 4 subdural hematomas, 2 brain hemorrhages, 1 retroperitoneal hemorrhage and 1 arterial bleed as a complication of paracentesis for relief of ascites. Half of the GI hemorrhage episodes were associated with grade 3 or 4 thrombocytopenia and/or gastric ulcers. STI571 was discontinued in 2/6 cases of GI hemorrhages. With the exception of a patient with factor V deficiency, all episodes of brain hemorrhage or subdural hematoma occurred in patients with aggressive and rapidly progressive disease, which led to discontinuation of study drug and an immediate fatal outcome in 4 patients.

**Conclusions CML AP:**

The hematologic response rate was 63%, 28% complete. Major and complete cytogenetic responses were achieved in 21 % and 14% of patients. STI571 400-600mg/day was generally well tolerated. Therapy was discontinued for AE's in only 6% of patients. Hematologic toxicity and fluid retention (edema) were the two most frequent AE's. A comparable STI-571 safety profile was observed in ALL, AML and CML in LBC patients.

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### 11.3 Study 0110

**Title of study:** 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

**Study center(s):** United States 10, France 3, Germany 4, Italy 7, Switzerland 1, United Kingdom 3

**Study period:** First patient enrolled: 06 December 1999      Cut-off date: 30 October 2000

**Primary Objective:** To determine the rate of complete and major cytogenetic response to STI571 for patients with CML who were hematologically or cytogenetically resistant or refractory to interferon-alpha (IFN) therapy or intolerant of that therapy.

**Secondary Objectives:** To determine the rate and duration of complete hematologic response (CHR) and the duration of complete cytogenetic response and major cytogenetic response; to evaluate the safety profile of STI571; to assess improvement in symptomatic parameters; to evaluate the basic pharmacokinetic (PK) characteristics of STI571 and its metabolite(s) and to evaluate the population pharmacokinetics (PK) of STI571.

**Inclusion criteria:** Male or non-pregnant female patients 18 years of age with Ph+ CML in the chronic phase (see above). ECOG performance status <3.

**Investigational drug:** STI571 was supplied as 100 mg capsules. Patients received 400 mg STI571 orally once daily.

**Statistical methods:** This protocol followed a single stage procedure design according to Fleming (alpha=2.5% (one-sided) and power=90%). For hematologic failures the hypotheses were: H0: p 10% and H1: p 20%. For cytogenetic failures the hypotheses were: H0: p 15% and H1: p 30%. All 95% confidence intervals (CI) were calculated using Pearson-Clopper limits. Time to event variables were evaluated using the Kaplan-Meier method.

**Efficacy Results:** The overall (unconfirmed) major cytogenetic responses was 49.4% (CI95% 45.1-53.8). The overall confirmed) major cytogenetic response rate was 38.0%. Complete cytogenetic response was seen in 30.1% and 14.7% of patients, unconfirmed and confirmed, respectively. The median time to major cytogenetic response was 2.89 months. The median duration of major cytogenetic response has not yet been achieved. The overall complete hematologic response rate was 88.0% (CI95% 84.9-90.6). It is too early to estimate the median duration of hematologic response.

**Safety:** STI571 was well tolerated, with the incidence of suspected study drug-related adverse events in any area based on body system less than or equal to 50%. Severe adverse events (Grades 3/4) or those reported as serious or clinically significant, were seen in less than one-third of all patients. Only 2.4% of patients had to discontinue therapy because of any adverse events. One patient died during study due to myocardial infarction. Four deaths were reported within 28 days after study discontinuation: Three were attributed to progression of leukemia and one patient died due to septic shock. A total of approximately 93% of patients overall continue on study.

**Conclusions:** A major unconfirmed cytogenetic response occurred in 36% of hematologic failure, 51% of cytogenetic failure and 58% of interferon intolerant patients. 88% of all patients had a complete hematological response, with 82.9% achieved within the hematologic failures and 93% within the cytogenetic failures. STI571 was generally well tolerated, enabling chronic oral daily administration of 400 mg doses in

this patient population, and requiring discontinuation due to AEs associated with study drug in only 1.3% of patients. Five patients died during the study or within 28 days of last dose, and in all but one case (myocardial infarction) the deaths were attributed to disease progression or complications of the underlying disease.

## 12.0 FDA Comments and perspective regarding study results

### 12.1 Study 0102

There is no effective therapy for patients with myeloid blast crisis CML. Treatment has included aggressive combination chemotherapy regimens similar to those used in the treatment of AML and stem cell transplantation. A summary of representative treatment results is provided in Table 83.

**Table 83 Literature treatment results-blast crisis**

No. of pts	Treatment	HR [N(%)]	MCyR [N(%)]	Median survival (mo)	Reference
195	AML-like regimens	44 (23)	--	4.5	6
24	Ara C, Daun	8 (33)	5 (21)	8	7
5	--	1 (20)	0 (0)	3.5	7
43	AraC	9 (21)	--	--	8

The 26% hematologic remission rate achieved with STI571 is comparable to results summarized in Table 83. Perhaps a more important indicator of efficacy, however, was the cytogenetic response rate. Using the most conservative figures from the FDA analysis ( 20 metaphases evaluated for each cytogenetic evaluation and cytogenetic response confirmed by at least two consecutive evaluations 1 month apart) there were 11 patients (4%) with a major cytogenetic response. Using less conservative estimates, i.e. irrespective of number of metaphases evaluated and/or unconfirmed by a second evaluation, there were 35 major cytogenetic responders (14%).

STI571 treatment was also associated with an improvement in symptomatology and in performance status in some patients. These analyses are preliminary and cannot be statistically analyzed.

### 12.2 Study 0109

Therapy for accelerated phase CML remains unsatisfactory. Treatments offered include high dose interferon, hydroxyurea and AML type regimens. Typical results are summarized in Table 84.

**Table 84 Literature treatment results-accelerated phase**

No. of pts	Treatment	HR [N(%)]	MCyR [N(%)]	Median survival (mo)	Reference
61	Various	32 (52)	4 (7)	--	8
24	Ara C, Daun	6 (25)	2 (8.5)	8	7

A difficulty with historical control comparisons of accelerated phase treatment results is absence of standardized criteria for that diagnosis. The various criteria for classifying patients as having accelerated phase disease are listed below.

**Definition of Accelerated-Phase Chronic Myelogenous Leukemia**

**M.D. Anderson Cancer Center**

Peripheral blood blasts 15%  
Peripheral blood blasts and promyelocytes 30%  
Peripheral blood basophils 20%  
Platelet count 100 cells X 10<sup>9</sup>/L unrelated to therapy  
Cytogenetic karyotypic evolution

**Criteria of Sokal and colleagues**

Peripheral blood or marrow blasts 5%  
Basophils > 20%  
Platelet count 1000 cells X 10<sup>9</sup>/L despite adequate therapy  
Karyotypic evolution  
Frequent Pelger-Huet-like neutrophils; nucleated erythrocytes; megakaryocyte nuclear fragments  
Marrow collagen fibrosis  
Anemia or thrombocytopenia unrelated to therapy  
Progressive splenomegaly  
Leukocyte doubling time < 5 d  
Fever not otherwise explained

**International Bone Marrow Transplant Registry Criteria**

Leukocyte count difficult to control with busulfan or hydroxyurea therapy  
Rapid doubling time of leukocytes (<5 d)  
Peripheral blood or marrow blasts 10%  
Peripheral blood or marrow blasts and promyelocytes 20%  
Peripheral blood basophils and eosinophils 20%  
Anemia or thrombocytopenia unresponsive to busulfan or hydroxyurea therapy  
Persistent thrombocytosis  
Karyotypic evolution  
Progressive splenomegaly  
Development of chloromas or myelofibrosis

The 63% hematologic remission rate achieved with STI571 is at least comparable, and possibly better, to results summarized in Table 84. As was the case in study 0102 a more important indicator of efficacy was the cytogenetic response rate. Using the most conservative figures from the FDA analysis ( 20 metaphases evaluated for each cytogenetic evaluation and cytogenetic response confirmed by at least two consecutive evaluations 1 month apart) there were 24 patients (9%) with a major cytogenetic response including 10 patients with a complete cytogenetic response. Using less conservative estimates, i.e. irrespective of number of metaphases evaluated and/or unconfirmed by a second evaluation, there were 50 major cytogenetic responders (19%).

STI571 treatment was also associated with an improvement in symptomatology and in performance status in some patients. These analyses are preliminary and cannot be statistically analyzed.

### 12.3 Study 0110

Over the course of several meetings with the sponsor the FDA raised concerns about the design and interpretation of the chronic phase CML study.

Regarding the eligible patient population the FDA indicated that hematologic resistance, i.e. 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 and cytogenetic resistance, i.e. bone marrow cytogenetics showing 65% Ph+ after one year of IFN-based therapy would generally be considered stable disease and not a reason to discontinue IFN treatment. The inclusion of these patients makes it difficult to compare study results with published trials.

A second issue concerned study endpoints. The FDA questioned whether MCyR rate is an acceptable surrogate for accelerated approval. The claims that MCyR rate is a surrogate for survival are based on analyses of whether patients receiving a particular treatment and achieving a MCyR live longer than patients who do not. In such an analysis there is no way to ascertain whether MCyR is an independent factor for survival prolongation or whether it is simply a marker for patients who will live longer. Both MCyR patients and non-MCyR patients got the same treatment. Thus treatment can not be the only factor and whether treatment is a factor at all can not be ascertained from this type of analysis.

To evaluate results of study 0110 the best comparator group might be randomized first-line interferon studies. These studies enrolled early chronic phase CML patients whereas 0110 enrolled late chronic phase CML patients who might be expected to have worse outcomes. As is evident in Table 85, in all trials except the Guilhot trial of Interferon + ara C the major cytogenetic response rate was <20%. In study 0110 the most conservative results from the FDA analysis ( 20 metaphases evaluated for each cytogenetic evaluation and cytogenetic response confirmed by at least two consecutive evaluations 1 month apart) were 186 patients (35%) with a major cytogenetic

response including 84 patients with a complete cytogenetic response. Using less conservative estimates, i.e. irrespective of number of metaphases evaluated and/or unconfirmed by a second evaluation, there were 265 major cytogenetic responders (50%).

**Table 85 Literature treatment results-chronic phase**

Study	Pts	Rx	CHR %	Time	MCR %	CCR %	Time mo	Surv
Guilhot 1997 (3)	360	I+H+A	66	Best	41	15	12	3y 86%
	361	I+H	55	Best	24	9	12	3y 79%
Italian 1994 (5)	218	I	HR 45	3 mo	19	8	Best	mst 72 m
	104	H or B	HR 46	3 mo	1	0	Best	mst 52 m
			HR 62	8 mo				
			HR 53	8 mo				
UK 1995 (1)	293	I			11	6	Best	Mst 61 m
	294	H or B			3	0	Best	Mst 41 m
German 1994 (4)	133	I	31	Best		7	Best	Mst 66 m
	186	B	23	Best		0	Best	Mst 45 m
	194	H	39	Best		1	Best	Mst 56 m
Ohnishi 1995 (9)	80	I	39	Best	17	9	Best	5y 54%
	80	B	55	Best	5	3	Best	5y 32%
Benelux 1998 (2)	100	I+H	51	6 mo	16	9	Best	Same
	95	I	29	6 mo	2	0	Best	

In all 3 trials safety was acceptable. See section 9.4 for serious adverse events.

## 13.0 References

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## **14.0 Use in Special Populations**

### **Pediatric Use**

The safety and effectiveness of STI571 in pediatric patients have not been established.

### **Geriatric Use**

In the clinical studies, approximately 40% of patients were older than 60 years and 10% older than 70 years. There was no difference in the safety profile in patients older than 65 years as compared to younger patients, with the exception of a higher frequency of mild to moderate, but not severe superficial edema. The efficacy of STI571 was similar in all age groups studied. Older patients (age 65 years) appear to exhibit higher probabilities of developing Grade 3 or higher, fluid retention.

### **Gender**

There was no important clinical difference in STI571 efficacy or safety by sex although older females may be at higher risk for developing CTC grade 1/2 edema than older males.

### **Ethnicity**

894 of 1027 patients (87%) participating in the clinical studies were caucasian.

### **Renal and Hepatic Impairment**

See study eligibility criteria.

## **15.0 120 Day safety update**

Given the short time between data submission and review a safety update will not be required prior to approval. A safety update will be submitted in May, 2001. Updated survival data will also be submitted at that time.

## 16.0 ODAC

NDA 21-335 will not be presented to ODAC. A regulatory decision will likely be made prior to the June, 2001 meeting.

## 17.0 Reviewer recommendation

I recommend Accelerated Approval, Subpart H, CFR§314.510, for all 3 phases of the CML disease process based on the surrogate endpoints of hematologic response (accelerated phase and blast crisis disease) and cytogenetic response (chronic phase disease).

As part of the phase 4 commitment the following should be done:

1. Completion of \_\_\_\_\_ with Time to Progression (TTP) as the primary surrogate endpoint. TTP is defined as:
  - Loss of CHR
  - Loss of cytogenetic response
  - Inability to maintain peripheral blood counts
  - Increasing organomegaly
  - Accelerated phase CML
  - Blast crisis
  - Death from CML
2. Completion of \_\_\_\_\_ a phase I study in children with refractory/relapsed Ph+ leukemias.
3. A phase II efficacy study must then be done in an appropriate pediatric population.
4. Continued follow-up for studies 0102 and 0109. Response duration and survival data might indicate sufficient clinical benefit so that full approval can be considered.
5. Continued follow-up of study 0110, especially the hematologic and cytogenetic refractory and interferon intolerant patient populations. Response duration and survival data might indicate sufficient clinical benefit so that full approval can be considered.
6. Physician and patient education programs regarding use of concomitant medications with STI571 (CYP 3A4 and 2D6 interactions).

/S/  
Martin H. Cohen, M.D.  
April 26, 2001

/S/  
Grant Williams, M.D.