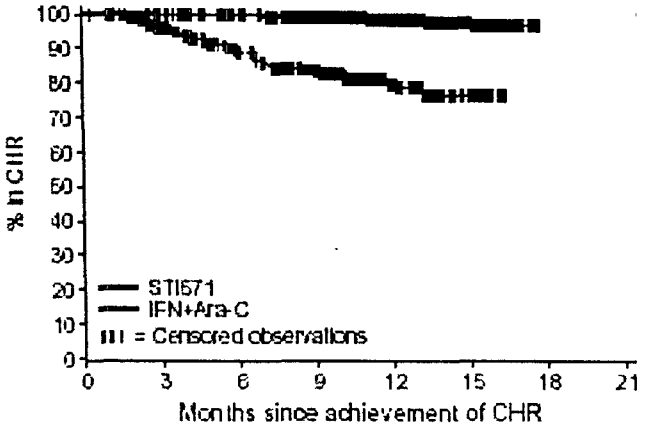
Figure 8: Sponsor's analysis of duration of Complete Hematolgic responses



Median duration of complete hematolgic response was not reached. The sponsor's analysis of the duration of complete hematologic responses is summarized in the table below:

Table 30: Sponsor's Summary for Duration of CHR

	Gleevec (n=553)	IFN+Ara-C (n=553)
No. of patients with confirmed CHR	522	302
No. of patients who lost CHR	11 (2.1%)	46 (15.2%)
Estimated % [95% CI] still in response at 6 months	99.4% [98,100]	89.5% [85,94]
Estimated % [95% CI] still in response at 9 months	98.8% [97,100]	83.6% [78,89]
Estimated % [95% CI] still in response at 12 months	98.0% [96,100]	79.7% [73,86]

Hematologic responses appear to be at least as durable in the Gleevec arm compared with the interferon arm.

11.2.4 Conclusions

There were relatively minor differences between the FDA estimated CHR rates and the sponsor's reported CHR rates. The sponsor and FDA agree that a statistically significantly higher proportion of chronic phase CML patients achieved a complete hematologic response (CHR) with Gleevec compared with interferon and Cytarabine. This difference could not be attributed to intolerance and toxicity of the interferon causing early crossover. Hematologic responses appeared to occur more quickly and appeared to be at least as durable on Gleevec compared with interferon and Cytarabine. A higher percentage of patients who crossed over from interferon to Gleevec achieved a response compared with those who crossed over from Gleevec to interferon, although definitive comparisons can not be made regarding the second line treatment groups since they were not randomly allocated between the groups. Although median duration of

complete hematolgic response was not reached, complete hematologic responses appear to be at least as durable on the Gleevec arming as with the interferon arm.

11.3. Time to Accelerated Phase or Blastic Phase

Time to accelerated phase or blastic phase will be analyzed separately, since the FDA regarded this endpoint as predictive of clinical benefit. CML in chronic phase may last 3 to 6 years, however patients who go into accelerated phase have a median survival of only 1 to 1.5 years, and in blastic phase, 3 to 6 months. An improvement in time to accelerated phase may therefore be reasonably likely to predict an improvement in survival.

Accelerated phase is defined as the appearance of one or more of the following:

- blasts in the blood or bone marrow $\geq$ 15%, and < 30% or
- percentage of blasts plus promyelocytes in the peripheral blood or bone marrow $\geq$ 30%, or
- peripheral basophils $\geq$ 20%o, or
- thrombocytopenia $\leq$ 100 x 10'/L unrelated to therapy.

Blastic phase is defined as the appearance of one or more of the following:

- blasts in the blood or bone marrow $\geq$ 30% or
- Appearance of extramedullary involvement (e.g. chloromas), except for liver and spleen.

To progress on the basis of an accelerated phase a patient could not subsequently exhibit a CHR.

The sponsor considered all thrombocytopenia while on therapy to be therapy-related. All patients with blast crisis fulfilled criteria for accelerated phase, therefore the analysis for time to accelerated phase and time to blast crisis were combined and a separate analysis of time to blast crisis was not conducted. Progression to accelerated phase events are summarized in the table below:

Table 31 Progression events to accelerated phase, first line and ITT

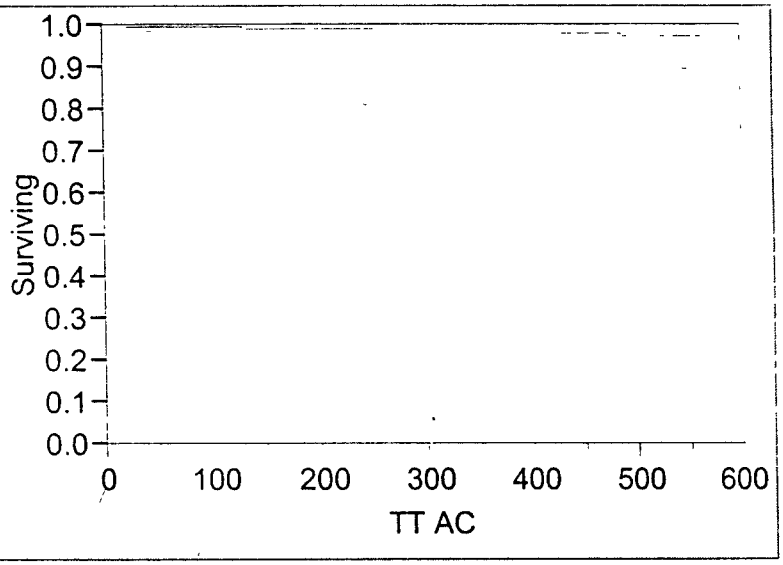
Progression to accelerated phase		Gleevec N (%)	IFN+Ara-C N (%)
Sponsor	First line	8 (1.4)	29 (5.2)
	ITT	10(1.4)	36 (5.8)
	Log-rank test (ITT)	p<0.001	
FDA	First Line	8 (1.4)	31 (6.0)
	ITT	10 (1.8)	38 (6.8)
	Log-rank test (ITT)*	P<<0.001	

* Of hazard ratio

Differences between FDA and sponsor were minor. These included one patient who was said to have progressed by an investigator but the data was not provided; one patient who progressed 5 days after crossing over from interferon to Gleevec, and the FDA reviewer determined that a progression should be ascribed to interferon; and one patient who had reached criteria for

accelerated phase but the investigator ascribed a complete hematologic response. The Kaplan-Meier plot of the time to accelerate phase of the FDA ITT data (in days) is reproduced in figure 9 below.

Figure 9: FDA Univariate survival plot of time in days to AP (ITT)



1= Gleevec (Top)
2=Interferon + Ara-C

Univariate analyses of the first-line as well as ITT times to accelerated phase by treatment group using JMP statistical software are summarized in Table 30:

Table 32: FDA Time to Accelerated Phase Analysis

First- Line		
Group	**N Failed**	**N Censored**
1 (Gleevec)	8	545
2 (IFN)	31	522
Significance Test	Log-Rank	P <.0001
	Wilcoxon	P <.0001
Intent to Treat		
Group	N Failed	N Censored
1 (Gleevec)	10	543
2 (IFN)	38	515
Significance Test	Log-Rank	P <.0001
	Wilcoxon	P <.0001

The FDA statistical reviewer estimated that the Gleevec vs. IFN+Cytarabine hazard ratio of the risk of progression to accelerated phase in the ITT population was 0.239 (95% C.I. of (0.119, 0.482)) and the log-rank test p-value was <0.001. The results are highly statistically significant in favor of the Gleevec treatment arm. The results of the sponsor and FDA analysis of progression to accelerated phase on second line treatment are summarized below:

Table 33: Progression to Accelerated Phase on second line treatment

Second-line treatment	Gleevec > IFN+Ara-C	IFN+Ara-C > Gleevec
Patients starting second-line treatment	N=7	N=218
N (%) progression to accelerated phase	2 (28.6)	5 (2.3)

Seven patients crossed over from the Gleevec to the interferon arm. Of these patients, 29% progressed into accelerated phase. Two hundred eighteen patients crossed over from interferon onto Gleevec, and of these, 5 patients (2.3%) progressed into accelerated phase. Because of the imbalance in crossovers, no conclusions can be made concerning the comparative efficacy of Gleevec versus interferon as a second line treatment.

Conclusions: An increase in the time to accelerated phase in patients with CML was considered by the FDA to be a predictor of improved survival and therefore a clinical benefit. The sponsor and FDA agree that a significantly higher percentage of patients progressed to accelerated phase on the interferon treatment arm compared with the Gleevec treatment arm, and that was true in both the first line as well as the intent to treat (ITT) analyses. The ITT analysis analyzed patients on the basis of the original treatment assignment. Despite a high percentage of crossovers to the Gleevec arm, a treatment difference was still apparent in the ITT analysis with a much higher percentage of patients progressing to accelerated phase who began treatment on the interferon arm compared with those who began treatment on the Gleevec arm.

11.4. Time to Progression (TTP): (Primary Efficacy Endpoint)

Time to progression was the amended primary objective of the study, and was defined as time from randomization to:

- Death
- Accelerated phase, blast crisis,
- Loss of CHR or MCR ,
- Increasing WBC counts in patients who did not achieve CHR, (certified by the study monitoring committee)

Reviewer comment: This was a complex endpoint to review. Patients who went into accelerated phase who subsequently went into CHR were not counted as having gone into accelerated phase. Patients who were designated as losing CHR had to have a previous CHR confirmed by 2 visits at lease 28 days apart as well as subsequent loss of CHR by 2 visits at least 28 days apart while on maximum tolerated therapy. Progressions due to increasing WBC counts were counted if the

study monitoring committee (SMC) agreed to crossover for these patients. The primary analysis was to be done on the intent to treat principle; therefore, excessive crossovers could potentially affect the study results.

11.4.1 Time to Progression, ITT principle

According to the sponsor, a total of 127 patients (24 on Gleevec and 103 on IFN + Ara- C) progressed during the study. Of these patients, 10 and 36 progressed to AP or BC in the two treatment groups respectively (2 patients on IFN + Ara- C with ' Loss of CHR' later progressed to AP). The sponsor's summary of overall progression events are summarized in the table below:

Table 34: Sponsor's Summary of TTP Events (ITT principle)

	Gleevec (n=553)	IFN+Ara-C (n=553)
Total number of progression events (ITT)	**24 (4.3%)**	**103 (18.6%)**
Progression to accelerated phase or blast crisis	8	32
Loss of CHR	6	39
Loss of MCyR	4	6
Increase in WBC (approved by SMC)	2	24
Death during treatment	4	2
Total number of patients with progression to AP or BC	**10 (1.8%)**	**36(6.5%)**
Total number of progression events (first line)	**22 (4.3%)**	**94 (17.4%)**

The sponsor's summary of progression events on Gleevec (based on ITT) is as follows:

- 10 progressions to AP/BC (in Table 31 two of these patients were listed as 'Loss of MCyR' and 'Increase in WBC' respectively as these were the patients' first events)
- 6 loss CHR (another 6 patients lost CHR and progressed to AP/BC at the same time, therefore were counted as AP/BC)
- 3 loss MCyR (another 3 patients lost MCyR and progressed to AP/BC at the same time, therefore were counted as AP/BC + one patient had lost MCyR on first-line and then progressed to AP/BC on second-line >>> now counted as AP/BC but included in Table 31 as 'Loss MCyR')
- 1 increase in WBC (one patient had increased WBC on first-line and then progressed to AP/BC on second-line >> now counted as AP/BC but included in Table 31 as 'Increase in WBC')
- 4 patients died during treatment

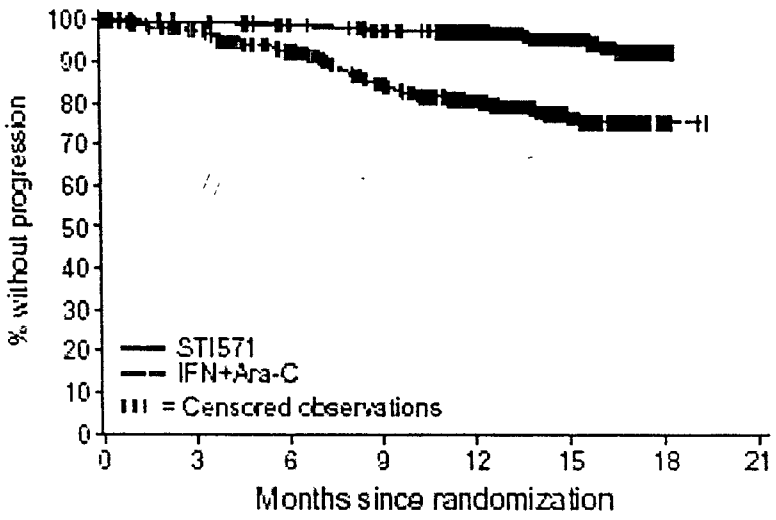
The sponsor's summary of progression events on IFN+Cytarabine (based on ITT) is as follows

- 36 progressions to AP/BC (29 on first-line, 2 on first-line after loss of CHR, 3 on second-line and 2 on second-line after loss of CHR >>> therefore 4 AP/BC events were included as 'Loss CHR' as these were the patients' first event)
- 35 loss CHR (as described above, 2 lost CHR on first-line and 2 lost CHR on second-line before they progressed to AP/BC >>> now counted as AP/BC but included as 'Loss CHR')

- 6 loss MCyR (another 3 patients lost MCyR and progressed to AP/BC at the same time, therefore were counted as AP/BC already)
- 24 increase in WBC (4 patients had increase in WBC but only after 'Loss of CHR' already, another three patients were considered in this category as they had increasing WBC and discontinued with reason 'Unsatisfactory therapeutic effect' instead of cross-over: patients 0141_00016, 0715_00001 and 0769_00006)
- 2 patients died during treatment

Since patients could experience more than one progression event simultaneously, the number of total progression events exceeded the number of patients who progressed. The sponsor's Kaplan-Meyer progression plot is reproduced in Figure 6:

Figure 10: Sponsor's TTP analysis (ITT Principle)



The FDA results of progression events are presented in the table below:

Table 35: FDA Summary of TTP Events (ITT principle)

	Gleevec N=553 (%)	IFN+Cytarabine N=553 (%)
Total no. of patients with events (progression)	**25 (4.5)**	**119 (21.5)**
Progression to accelerated phase or blast crisis	8 (1.8)	33 (5.9)
Loss of CHR	6 (1.1)	38 (6.8)
Loss of MCyR[a]	4 (0.7)	6 (1.1)
Increase in WBC [b]	2 (0.4)	25 (4.5)
Death during treatment	4 (0.7)	2 (0.4)

[a] and no other reason for progression

[b] FDA exploratory analysis – pts with 5 visits with WBC> 20

These were the initial progression events, and since patients could satisfy different criteria for progression on different days, the total number of progression events exceeded the number of TTP events (see Table 29). The FDA identified an additional patient who progressed into accelerated phase on the interferon arm (see discussion of time to accelerated phase results, section 11.3). The FDA was able to verify the sponsor's loss of CHR results and loss of MCyR results. Since progressions on the basis of increasing WBC were certified for crossover by the study monitoring committee, and the treatment arms were not blinded, progressions on the basis of increasing WBC may have been subject to bias. In an exploratory analysis, the FDA identified 27 patients who were designated as having progressed on the basis of increased WBC's on the 5th visit with a WBC greater than 20; 2 on Gleevec and 25 on interferon. This was comparable to the 26 patients identified by the study monitoring committee as having progressed due to increasing wbc's: 2 on Gleevec and 24 on interferon. Ten of the patients were the same patients identified by the study monitoring committee during the trial, and 17 were different patients, but the overall numbers in each treatment arm were quite similar for each progression category except for survival, the interferon arm was observed to have more progression events than the Gleevec arm.

The FDA medical reviewer's univariate analysis of time to progression (in days) is shown in Figure 11:

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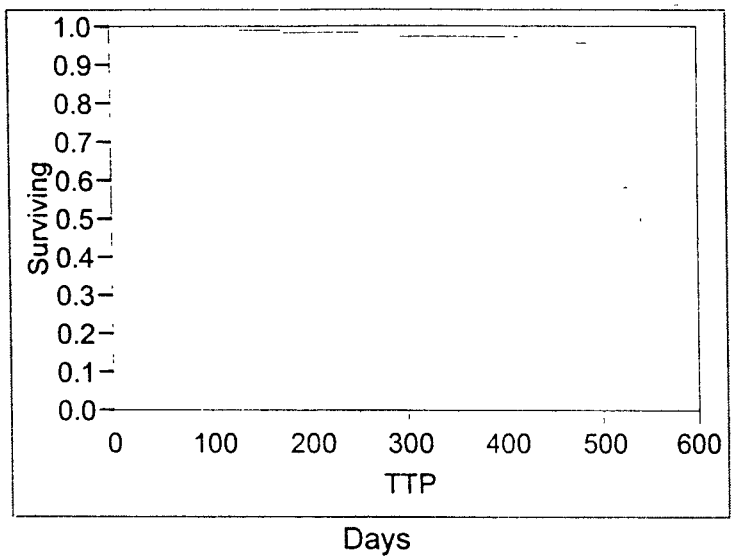
Figure 11: FDA Univariate Time to Progression (ITT)



1=Gleevec (top)
2= Interferon (Bottom)

Table 36:FDA analysis of time to progression (ITT population)

	Gleevec N=553	IFN+Ara-C N=553
No. of events	24 (4.3%)	103 (18.6%)
Log-rank test Wilcoxon test	P <.0001 p<.0001	

At the time of this analysis, there were 127 events of progression and the FDA agreed with the sponsor that the TTP results are quite highly statistically significant favoring the Gleevec arm. The FDA statistical reviewer estimated that the Gleevec vs. IFN+Cytarabine hazard ratio was 0.183 (95% C.I. of 0.117, 0.285) and the log-rank test p-value is much less than 0.001. The planned cutoff date for the TTP analysis was the date of the 385th event. The FDA statistical reviewer performed an exploratory model to attempt to predict the theoretical possibility of the study failing to reject the null hypothesis that the time to progression was no different on either arm. If for the remaining 258 events needed for the protocol defined final analysis, the theoretical hazard ratio is 1, then the chance of rejecting the null hypothesis that the two theoretical distributions for TTP are the same (and favoring Gleevec) is roughly 96.9%. At the beginning of the trial, if the theoretical hazard ratio is 1 then, after 385 events, the chance of rejecting the null hypothesis that the two theoretical distributions for TTP are the same (and favoring Gleevec) is 2.5%.

Reviewer comment: The progression endpoint was complex. For a patient to progress on the basis of loss of CHR the patient had to satisfy criteria for CHR for at least 28 days and

subsequently satisfy criteria for loss of CHR on at least 2 occasions while on maximum tolerated therapy. Several patients met multiple criteria for progression on the same day or different days.

Conclusions: The planned cutoff date for the TTP analysis was the date of the 385th event, however the progression analysis was performed early because of the highly significant results of the interim analysis of cytogenetic response at one year. FDA and the sponsor agree that the interim analysis of TTP results at 127 progression events are quite highly statistically significant, favoring the Gleevec treatment arm. The Gleevec vs. IFN+Cytarabine hazard ratio was 0.183 (95% C.I. of 0.117, 0.285) and the log-rank test p-value is much less than 0.0000001. Analysis of the Kaplan-Meier plot confirms that the Gleevec treatment arm has a statistically significantly longer time to progression than the interferon treatment Arm.. Statistical modeling suggest that it is probable that the results will still be statistically significant favoring the Gleevec treatment arm at 385 events.

11.5. Survival

With a median follow-up of 14 months (up to a maximum of 19.5 months), there were a total of 31 deaths: 11 in patients randomized to Gleevec (1 of them after crossover to IFN) and 20 on the IFN + Cytarabine arm (4 of them after crossover to GLEEVEC and another 5 after documented extension treatment with GLEEVEC). Causes of Death are summarized in the following table:

Table 37: Deaths on study, ITT population

Cause of Death	Gleevec	IFN + Ara-C
CML related	5	13
Deaths after BMT (from CML related)	1	2
not CML related	6	7
All deaths	11 (2.0%)	20 (3.8%)

The FDA statistical reviewer estimated the hazard ratio for death from any cause in the Gleevec vs Interferon treatment arms was 0.559 with corresponding 95% CI of (0.267, 1.171). Differences in survival between arms were not statistically significant with the log-rank p-value of 0.1169. Causes of death are discussed further in the safety review. The median survival of CML patients historically is around 6-8 years. Extensive crossover may make survival results difficult to interpret. If treatment with Gleevec prolongs survival on both arms due to extensive crossover population, the median survival is not likely to be reached in 5 years.

Conclusions: There was no statistically significant difference in survival between treatment arms at the time of analysis. Median survivals are unlikely to be reached until at least five years of follow-up.

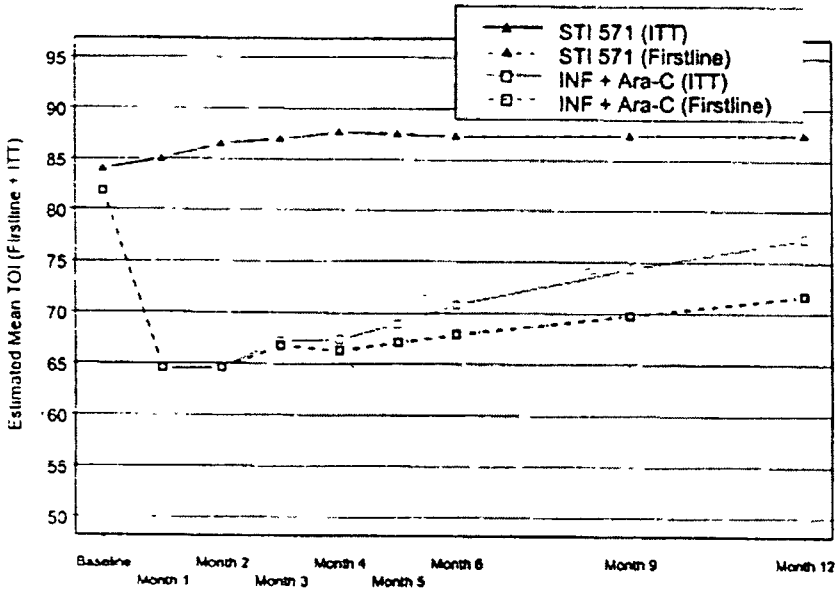
11.6. QOL Assessments:

A patient reported symptom assessment was performed at baseline, monthly for the first six months of therapy, and then at the end of 9, 12, 18 and 24 months. The instrument used was the Functional Assessment of Cancer Therapy biologic response modifier (FACT-BRM) questionnaire, consisting of a general quality of life instrument with physical, functional, emotional, and social modules, and two treatment-specific BRM modules. The primary patient

reported outcome (PRO) endpoint was the treatment outcome index (TOI), consisting of 27 items which made up the physical and functional well-being subscales and the treatment specific subscales. The primary aim of this PRO study was to compare the Trial Outcome Index (TOI) in the 2 treatment groups. The TOI is a composite endpoint derived from the Functional Assessment of Cancer Therapy measurement tool. The TOI includes all the scales in the FACT-BRM instrument except for the social/family and emotional well-being scales.

The sponsor's analysis of TOI results is shown in Figure 12 below:

Figure 12: Sponsor's Trial Outcome Index (TOI) analysis by treatment group



Since the TOI analysis used the ITT approach, the increasing scores on the interferon arm at 9 and 12 months could be attributable either to tolerance to the medication, or to large numbers of IFN patients who crossed over to the Gleevec arm and began to report increased TOI scores on Gleevec. The TOI scores and numbers of patients surveyed are summarized in the following table:

Table 38:Baseline adjusted Trial Outcome Index (TOI) FACT-BRM scores

	Gleevec		IFN + Ara-C	
	N (first-line/ITT)	Mean Score	N (first-line/ITT)	Mean Score
Base line	492/492	83.58	484/484	81.35
Month 1	483/483	84.16	434/435	64.62
Month 6	469/469	86.58	313/381	68.55
Month 12	422/424	87.19	167/313	77.95

Initial baseline TOI scores prior to randomization approached statistical significance in favor of the Gleevec treatment group. Subsequent differences between treatment groups were too large to be attributed to baseline differences in the populations. The TOI scores include the FACT-BRM questionnaire scores without the emotional and social well-being scales. A separate analysis of social and emotional well-being scales revealed small differences between treatment groups at months 1-12 in favor of Gleevec. The TOI instrument was designed to be a measurement of interferon-related toxicities, rather than global quality of life. The TOI instrument was designed to measure symptoms, which are commonly the result of interferon administration, such as fatigue, weakness, fevers, chills, and sweating. There were no questions about edema, characteristically a side effect of Gleevec treatment. The sponsor states in section 3.5.3.2 of the protocol, regarding quality of life efficacy measurement, that "FACT-BRM focuses on the impact of interferon-related toxicities on the functional and cognitive assessment of the patient." The TOI scale is therefore a measure of interferon toxicity rather than global quality of life.

Conclusions: The FDA analysis suggests that there may have been a slight baseline imbalance prior to randomization, in which patients on the Gleevec treatment arm reported fewer symptoms even prior to randomization. This difference was relatively small compared with the overall treatment effect. After one month of treatment, there were markedly increased differences in TOI scores between treatment arms. Patients commencing IFN + cytarabine treatment experienced a decrease in their TOI scores at one month and throughout the study compared with patients commencing Gleevec treatment. This decrease in TOI scores was consistent with an increase in symptoms of interferon-related toxicity. In comparison, patients on Gleevec treatment experienced no change in their TOI scores throughout the study. These results suggest that patients taking Gleevec experienced significantly fewer symptoms of interferon toxicity than patients taking interferon.

12 Efficacy Conclusions

The initial primary efficacy endpoint was time to treatment failure, but this was not acceptable to the FDA and the primary efficacy endpoint was amended to time to progression. The definition of progression included death during treatment, the development of accelerated phase or blast crisis, loss of complete hematologic or cytogenetic responses, and increasing white blood counts that were reviewed by the study monitoring committee and certified as therapeutic failures appropriate for crossover. The planned cutoff date for the TTP analysis was the date of the 385th event, however the progression analysis was performed early because of the highly significant results of the interim analysis of cytogenetic responses at one year. Patients may progress in more than one way, however the date a patient initially fulfilled any one of the progression criteria was used as the progression event date. The protocol specified that the progression analysis would compare the intent to treat (ITT) populations: patients randomized to receive Gleevec were compared with patients randomized to receive interferon. Patients that crossed over prior to progression were not censored at the time of crossover, and events that occurred in these patients following crossover were attributed to the original randomized treatment. A total of 218 patients (39%) crossed over from the interferon to the Gleevec arm, and

7 patients (1.3%) crossed over from the Gleevec to the interferon arm. The following table summarizes the sponsor's analysis of initial progression events observed in the trial.

Table 39: Sponsor's Summary of Progression Events (ITT principle)

	Gleevec N=553 (%)	IFN+Cytarabine N=553 (%)
Total number of progression events (ITT)	**24 (4.3%)**	**103 (18.6%)**
Progression to accelerated phase or blast crisis	8 (1.8)	32 (5.7)
Loss of CHR	6 (1.1)	38 (6.8)
Loss of MCyR[a]	4 (0.7)	6 (1.1)
Increase in WBC [b]	2 (0.4)	25 (4.5)
Death during treatment	4 (0.7)	2 (0.4)

[a] and no other reason for progression

[b] FDA exploratory analysis – pts with 5 visits with WBC> 20

FDA and the sponsor agree that the interim analysis of TTP results at 127 progression events are quite highly statistically significant, favoring the Gleevec treatment arm. The Gleevec vs. IFN+Cytarabine hazard ratio was 0.183 (95% C.I. of 0.117, 0.285) and the difference was highly statistically significant by log-rank test. Analysis of the Kaplan-Meier plot (Figure 11 and Table 33) confirms that the Gleevec treatment arm has a statistically significantly longer time to progression than the interferon treatment arm. Statistical modeling suggest that it is probable that the results will still be statistically significant favoring the Gleevec treatment arm at 385 events.

The FDA considered that a significant delay in time to accelerated phase was likely to result in a prolonged survival and was therefore an endpoint predictive of clinical benefit. The sponsor and FDA agree that a significantly higher percentage of patients progressed to accelerated phase on the interferon treatment arm compared with the Gleevec treatment arm, and that was true in both the first line as well as the intent to treat (ITT) analyses, despite the high percentage of crossovers to the Gleevec arm (Figure 9 and Table 30).

Secondary efficacy endpoints included complete hematologic response rate and duration, major cytogenetic response rate and duration, survival, and patient-reported "quality of life." The sponsor and FDA agree that a statistically significantly higher proportion of chronic phase CML patients achieved a complete hematologic response (CHR) with Gleevec compared with interferon and cytarabine. Onset of CHR appeared to be more rapid (Figure 7) and the responses appeared to be at least as durable on Gleevec compared with interferon and cytarabine (Figure 8) over the study duration. Although median duration of complete hematologic response was not reached, at the study conclusion 11 patients (2.1%) on Gleevec had lost their complete hematologic responses while 46 patients on interferon had lost their complete hematologic responses at data cutoff. All analyses of response rates favored the Gleevec treatment arm and were highly statistically significant. The sponsor's and FDA's analyses of confirmed CHR and cytogenetic response rates are summarized in the following Table:

Table 40:FDA and Sponsor's Confirmed Response Rates (ITT population)

Analysis	Gleevec N=553	IFN+Ara-C N=553
Complete Hematologic Response Rates		
Sponsor's CHR rate n (%)	523 (94.6%)	423 (76.5%)
95% CI	[92.3%, 96.3%]	[72.7%, 80.0%]
Fisher's Exact Test	p<0.001	
FDA CHR rate n (%)	534 (96.6%)	451 (81.5%)
Sponsor's Confirmed Cytogenetic Response Rates		
Number of MCyR (%)	419 (75.8%)	67 (12.1%)
95% C.I.	0.720-0.793	0.095-0.151
Fisher's Exact Test	< 0.001	
Number of CCyR	297 (53.7%)	15 (2.7%)
FDA Confirmed Cytogenetic Response Rates		
Number (%) confirmed MCyR	326 (59.0%)	41 (7.4%)
95% C.I.	54.7%, 63.1%	5.4%, 9.9%
Fisher's Exact Test	1.24×10^{-80}	
Number (%) confirmed CCyR	146 (26.4%)	18 (3.3%)
95% C.I.	22.8%, 30.3%	1.9%, 5.1%
Fisher's Exact Test	7.33×10^{-30}	

In the FDA's analysis of confirmed major cytogenetic responses, 59% of patients on Gleevec achieved a confirmed major cytogenetic response, compared with 7.4% on the interferon treatment arm. Over seven times as many patients attained a cytogenetic response on Gleevec compared with interferon and cytarabine and the results are highly statistically significant. In the FDA analysis of confirmed complete cytogenetic responses, 26.4 % of patients on Gleevec achieved a confirmed complete cytogenetic response, compared with 3.3% on the interferon treatment arm. FDA and sponsor results for both major cytogenetic responses and complete cytogenetic responses are both quite statistically significant favoring the Gleevec arm. The median time to major cytogenetic response was 3 months on Gleevec (range 2.2 to 17 months) and 8.4 months on interferon (range 2.8 to 16.4 months). The cytogenetic responses induced by treatment with Gleevec appear to be durable over the time period of study: eight percent of patients on interferon lost their major cytogenetic response compared with only 1.5% on Gleevec (Figures 5 and 6).

Several issues affected the interpretation of these results. The overall dose intensity of interferon achieved in study 106 was 56% of the target dose, compared with a 97% of planned dose intensity for patients on the Gleevec arm. A definite dose-response of interferon and cytarabine is difficult to establish, and a comparison of previous studies of interferon and cytarabine with study 106 is summarized in the following table:

Table 41: Dose Intensity of IFN and Cytarabine and Historical CML Response Rates

Study	IFN		Cytarabine		Response Rates 1 yr *	
	Dose intensity %	Mean dose Mu/day	% of pts receiving	Mean daily dose	CHR	MCyR
106	56%	5.04	70%	33.6	55 %	30%
Italian[23]	70 %	-	95%	-	62%	21%
French[24]	-	5.4	91%	30 mg	66%	35%%

* Unconfirmed

Overall the dose intensity of the active control arm appeared to be less than that achieved in previously published studies of interferon and cytarabine. Had the dose intensity of the active control arm have been higher, the CHR and MCyR response rates on the interferon and cytarabine arm might also have been somewhat higher. However, the best results of previous trials do not come close to the 95% CHR rates and 59% confirmed Major Cytogenetic Response rates results reported on the Gleevec arm of study 106. It is unlikely that the results would have been sufficiently different to come close to the 95% CHR and 84% MCyR rates reported on the Gleevec arm in study 106. Although it is not possible to predict what results would have been obtained given a different dose intensity, it seems reasonably likely to the FDA clinical reviewer that the Gleevec arm would have maintained a significant advantage over the interferon arm had a dose intensity had been achieved on the interferon arm equal to that obtained in historical trials with interferon and cytarabine in CML.

The most significant factor affecting efficacy results was the high degree of crossover allowed. Almost 40% of the patients who began on the Interferon/Cytarabine arm crossed over to the Gleevec arm, whereas only 1% of patients originally on the Gleevec arm crossed over to the Interferon/Cytarabine arm. This fact could cause an overestimation of the response rates in the active control arm, since the hematologic responses of patients who crossed over from interferon to Gleevec increased the responses rates attributed to the interferon arm. The CHR rates on the interferon arm were 54% and 76% in the sponsor's analysis of first line and the ITT populations, respectively; whereas Gleevec CHR rates were essentially unchanged at 94% between the two populations. Major Cytogenetic responses were similarly affected. The differences in ITT progression events would also tend to be obscured by extensive crossover, assuming that crossing over from interferon to Gleevec would significantly decrease the risk of progression. If all the interferon patients crossed over to the Gleevec arm, all the progression events would occur on the Gleevec arm. The extensive crossover would make survival results difficult to interpret, unless the initial few months of Gleevec therapy imparted a significant survival advantage.

FDA and sponsor analysis of CHR rates, major and complete cytogenetic response rates, as well as time to progression and time to accelerated phase or blast crisis all favored the Gleevec arm and were highly statistically significant in both the first line and ITT populations despite extensive crossover. Survival was not significantly different between arms but only 31 patients had died out of 1106 at the time of analysis and it is anticipated that median survival may not be reached for 5 or more years. Extensive crossover will hinder interpretation of long term follow-up results.

VII Integrated Review of Safety

1 Brief Statement of Conclusions

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

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

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

2 Description of Patient Exposure

The safety review is conducted using the electronic database from the randomized controlled trial comparing Gleevec and the combination of Interferon +Ara-C for initial treatment of CML in chronic phase. There are 1106 patients, 553 in each treatment arm.

The following Tables show the duration of exposure, daily dose and relative dose intensity (RDI) in both treatment groups.

Gleevec exposure was for a median of 421 days. Median relative dose-intensity (RDI) of Gleevec was near one and interferon was 0.57. The relative dose-intensity of cytarabine was impossible to determine because of the complex dose escalation scheme. Only 374 of 553 patients in the Interferon + cytarabine treatment group received cytarabine.

The FDA exposure analysis is consistent with the exposure analysis submitted by the Applicant.

Table 42:Treatment Duration (days)

	Median Duration	Mean Duration	Max Duration	Min Duration
Glv	421	411	563	5
Inf	239	259	554	1
Ara-C*	4	5.3	22	1

*Number of Ara-C Cycles

Table 43: Daily Doses of Treatment Received

	Median Dose	Mean Dose	Max Dose	Min Dose
Glv (mg)	400	386	717	114
Inf (MU/m2)	2.6	2.7	11.3	0.57
Ara-C (mg/m2)	19	17.7	27.3	2.2

Table 44: Relative Dose Intensity (RDI)

	Median RDI	Mean RDI	Max RDI	Min RDI
Glv	1	0.97	3.95	0.28
Inf	0.57	0.59	2.25	0.11
Ara-C	(Not able to asses)			

3 Methods and Specific Findings of Safety Review

The safety review was conducted by John Johnson, MD, using the electronic database from the randomized controlled trial comparing Gleevec and the combination of Interferon +Ara-c for initial treatment of CML in chronic phase. There are 1106 patients, 553 in each treatment arm. The number patients randomized to the Gleevec treatment group who were dosed is 551.

The FDA safety analysis is consistent with the safety analysis submitted by the Applicant.

3.1. Adverse Events

The following Tables show the per cent of patients with each adverse event for adverse events seen in ≥ 20% and ≥ 10% of patients in either treatment group. Adverse events are graded using the NCI Common Toxicity Criteria.

The only ≥ grade 3 Gleevec adverse events seen in > 1% of patients are neutropenia, thrombocytopenia and arthralgia.

Edema is seen in 54% of Gleevec patients, but is seldom greater than grade 2. The median duration of edema grade ≥ 2 in Gleevec patients is 64 days.

Table 45: Adverse Events In ≥ 20% of Patients First Line

Adverse Event	% Pts Glv N=553	% Pts Inf+Ara-c N=533	% Pts Glv G3	% Pts Inf+Ara-c G3	% Pts Glv G4	% Pts Inf+Ara-c G4
Nausea	42.5	60.8	0.4	5.1	0.0	0.2
Muscle cramps	33.4	8.6	0.7	0.2	0.0	0.0
Fatigue	30.7	64.9	1.1	24.0	0.0	2.1
Diarrhea NOS	30.3	40.9	1.3	3.2	0.0	0.0
Headache NOS	28.5	41.8	0.4	3.2	0.0	0.0
Arthralgia	26.5	38.3	2.2	6.8	0.2	0.9
Periorbital Edema	25.8	1.1	0.2	0.0	0.0	0.0
Myalgia	20.7	38.5	1.5	7.7	0.0	0.8
Rash NOS	20.0	14.4	1.3	1.1	0.0	0.0

The most commonly reported adverse events in the Gleevec treatment group were nausea, muscle cramps, fatigue, diarrhea, headache, arthralgia, periorbital edema, myalgia, and rash. The most commonly reported adverse events on the interferon arm were fatigue, nausea, headache, diarrhea, and myalgia. Edema was much more commonly reported in patients receiving Gleevec. Adverse events reported with a frequency of above 10% are summarized in the following Table:

Table 46: Adverse Events In ≥ 10% of Patients in Either Treatment Group First Line

Adverse Event	% Pts Glv N=553	% Pts Inf+Ara-c N=533	% Pts Glv G3	% Pts Inf+Ara-c G3	% Pts Glv G4	% Pts Inf+Ara-c G4
Nasopharyngitis	19.2	7.7	0.0	0.2	0.0	0.0
Oedema peripheral	15.8	3.9	0.2	0.0	0.0	0.0
Dyspepsia	15.1	9.2	0.0	0.8	0.0	0.0
Pain in limb	14.7	15.0	1.1	2.6	0.0	0.2
Vomiting NOS	14.7	26.6	0.9	3.4	0.0	0.2
Back pain	14.5	18.6	0.9	2.4	0.0	0.6
Pharyngolaryngeal pain	14.3	11.4	0.2	0.0	0.0	0.0
Dizziness	13.2	23.1	0.5	3.4	0.0	0.0
Cough	12.5	21.8	0.2	0.6	0.0	0.0
Upper respiratory tract infection NOS	12.5	8.1	0.2	0.4	0.0	0.0
Pyrexia	12.0	38.8	0.7	2.8	0.2	0.4
Insomnia	11.6	18.4	0.0	2.3	0.0	0.2
Weight increased	11.6	1.7	0.7	0.2	0.0	0.0
Abdominal pain NOS	10.3	10.3	1.1	1.9	0.4	0.0
Abdominal pain upper	9.6	12.4	0.5	1.5	0.2	0.0
Thrombocytopenia	9.3	25.0	5.3	12.0	0.2	0.9
Depression	8.9	34.7	0.5	12.4	0.2	1.7
Neutropenia	8.5	12.9	7.1	8.4	0.9	0.9
Bone pain	8.0	14.6	0.9	3.0	0.0	0.6
Constipation	7.6	13.9	0.7	0.2	0.0	0.0
Rigors	6.9	33.8	0.0	0.8	0.0	0.0
Anxiety NEC	6.5	10.9	0.2	2.6	0.0	0.4
Despond NOS	6.5	14.4	1 3	1.7	0.4	0.2
Pruritus NOS	6.5	11.4	0.2	0.2	0.0	0.0
Influenza like illness	6.4	18.4	0.0	1.1	0.0	0.0
Night sweats	6.4	15.0	0.2	0.4	0.0	0.0
Anemia NOS	5.4	11.3	1.3	3.9	0.4	0.2
Anorexia	4.7	31.3	0.0	2.4	0.0	0.2
Sweating increased	3.3	14.4	0.0	0.4	0.0	0.0
Alopecia	2.2	14.6	0.0	0.2	0.0	0.0
Weight decreased	2.2	16.9	0.0	1.1	0.0	0.0
Asthenia	1.6	10.9	0.0	1.9	0.0	0.0
Dry mouth	1.6	10.3	0.0	0.2	0.0	0.0
Mucosal inflammation NOS	0.7	10.1	0.0	3.2	0.0	0.2

The following two bar charts show the 11 most frequent adverse events on a per patient basis with Gleevec and alpha interferon + Ara-C, respectively.

Figure 13: Gleevec Top 11 AE's (% of Patients with each Event)

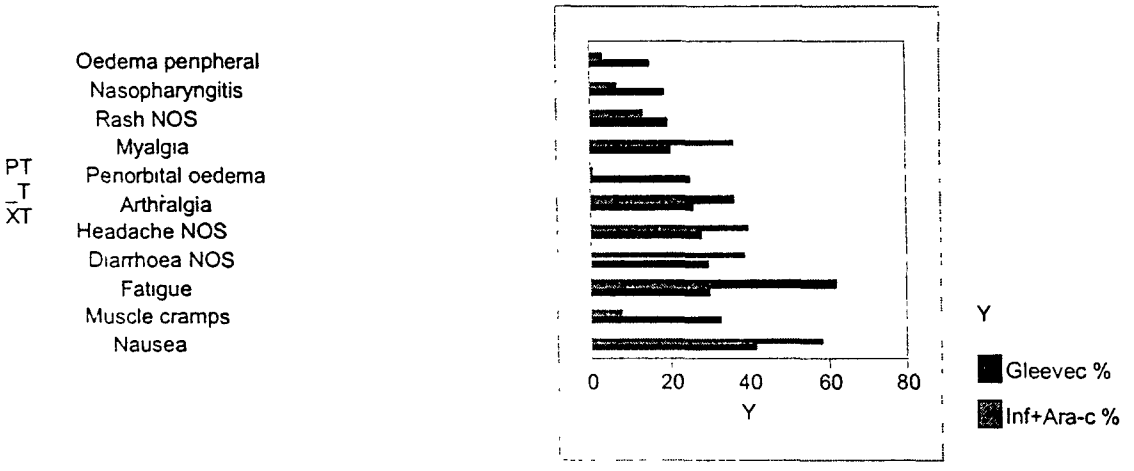
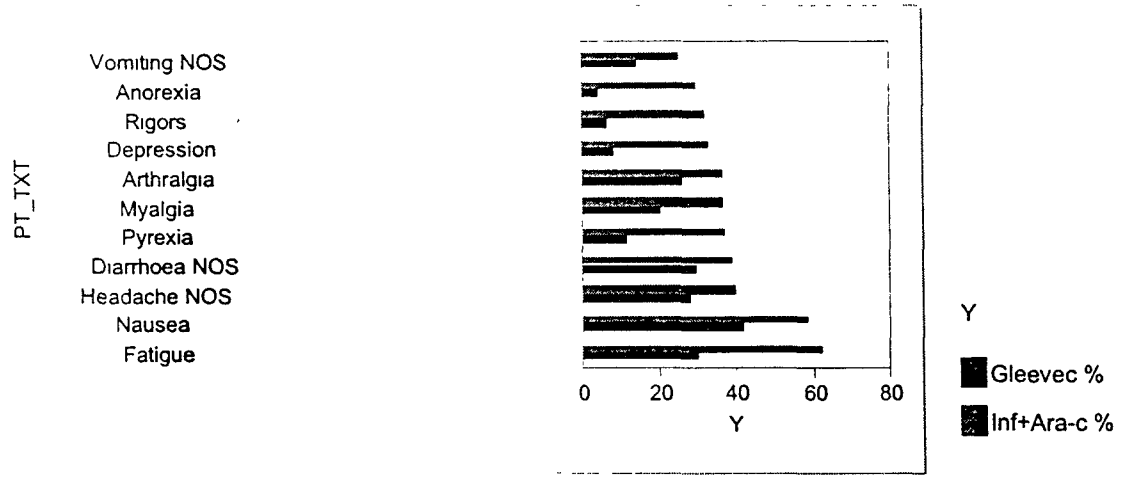


Figure 14: Interferon and Ara-C: Top 11 AE's (% of Patients with each Event)



The following Table shows the per cent of patients with edema in each treatment group. The median duration of edema grade ≥ 2 in Gleevec patients is 64 days.

Table 47: Percentage of Patients with Edema*

Treatment	Edema *	Edema* Grade 3	Superficial Edema	Superficial Edema Grade 3	Other Edema	Other Edema Grade 3
Gleevec	54.1	0.9	53.2	0.9	3.4	0.0
Inf+Ara-c	10.1	0.9	8.8	0.4	1.5	0.54

Superficial Edema = localized edema, face edema, periorbital edema, eyelid edema, peripheral edema
Other Edema = pleural effusion, pericardial effusion, ascites, pulmonary edema and anasarca
* Edema = Total of Superficial Edema and Other Edema

The following Table shows the per cent of patients with hemorrhage in each treatment group.

Table 48:Percentage of Patients with Hemorrhage

Treatment	All Grades	Grade 3	Grade 4
Gleevec	18.5	0.2	0.4
Inf+Ara-c	19.5	0.9	0.2

Grade 3 = Requiring transfusion

Grade 4 = Catastrophic bleeding, requiring major non-elective intervention

3.2. Deaths

The following Tables list the deaths in both treatment groups. Deaths in the Gleevec treatment group do not appear to be drug-related, with the possible exception of toxic epidermal necrolysis-Stevens-Johnson syndrome in one patient.

Table 49: Deaths Gleevec First Line

Pt #	Cause of Death	Survival (Months)
0003_00003	STUDY INDICATION	14.3
0016_00001	BRONCHUS CARCINOMA/|Bronchial carcinoma	12.0
0016_00002	PROBABLY CARDIAC ARREST/|Cardiac arrest	7.5
0050_00004	NEURO ENDOCRINE LIVER METASTASIS OF CANCER UNKNOWN ORIGIN./|Metastases to liver	13.9
0142_00004	STUDY INDICATION	4.8
0159_00003	CAR CRASH/|Road traffic accident	14.3
0708_00002	TOXIC EPIDERMAL NECROLYSIS -- STEVEN JOHNSON	1.3
0727_00009	STUDY INDICATION	4.5
0762_00003	ACUTE MYELOCYTIC LEUKEMIA/|Acute myeloid leukemia NOS	8.0
0765_00003	CARDIORESPIRATORY ARREST/|Cardio-respiratory arrest	10.3

Table 50: Deaths Inf/Ara-c First Line

Pt#	Cause Death	Survival (Months)
0032_00001	DISEASE PROGRESSION/Malignant neoplasm aggravated	6.0
0035_00001	STUDY INDICATION/|	13.4
0054_00008	STUDY INDICATION/|	13.7
0065_00012	TRAFFIC ACCIDENT/Road traffic accident	8.2
0075_00002	STUDY INDICATION/|	8.2
0142_00002	STUDY INDICATION/|	18.4
0147_00002	STUDY INDICATION/|	17.1
0150_00002	RECTAL CARCINOMA WITH LIVER METASTASES/Rectal cancer metastatic	18.1
0152_00009	STUDY INDICATION/|	7.4
0717_00005	CARDIOPULMONARY ARREST/|Cardio-respiratory arrest	10.3
0726_00001	STUDY INDICATION/|	4.8
0727_00006	PNEUMOCOCCAL SEPSIS/|Pneumococcal sepsis	12.8
0727_00013	MULTI ORGAN FAILURE/Multi-organ failure	10.7
0738_00016	FUNGAL SEPSIS/|Mycotic sepsis	8.1
0762_00005	PER REFERRING ONCOLOGIST CAUSE OF DEATH UNKNOWN/Death NOS	15.2
0764_00006	MULTI-ORGAN FAILURE/|Multi-organ failure	2.1
0766_00001	STUDY INDICATION/|	10.3
0766_00002	ACUTE MYOCARDIAL INFARCTION/Acute myocardial infarction	3 4

3.3. Discontinuations of First Line Treatment due to Grade 3 or 4 Toxicity

The following Tables show the number of patients discontinuing first line treatment for Grade 3 or 4 toxicity in each treatment group. Eleven Gleevec patients discontinued treatment for 28 kinds of grade 3 or 4 toxicity.

Table 51:Gleevec First Line Discontinuations for Grade 3 or 4 Toxicity

# Patients with each AE	Grade 3 or 4 AE
2	Alanine aminotransferase increased
1	Atrial fibrillation
1	Balance impaired NOS
1	Blood alkaline phosphatase NOS increased
1	Brain neoplasm NOS
1	Chest pain
2	Dizziness
1	Face Oedema
1	Hematotoxicity NOS
1	Hemoglobin decreased
1	Hypertension aggravated
1	Hypokalemia
1	Muscle cramps
1	Nausea
1	Neutropenia
1	Orthostatic hypotension
1	Prostate cancer metastatic
1	Prostate cancer NOS
1	Rash maculo-papular
2	Rash NOS
1	Small cell lung cancer stage unspecified
1	Stevens Johnson syndrome
1	Syncope
1	Urticaria NOS
1	Vision blurred

Grade 3-4 adverse events that led to the discontinuation of first line therapy in patients receiving interferon are shown in the following table. Thirty-four patients discontinued treatment with interferon for 164 kinds of grade 3/4 adverse events.

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Table 52: Inf/Ara-C First Line Discontinuations for Grade 3/4 Toxicity

# Patients with each AE	Grade 3 or 4 AE
1	Abdominal pain NOS
1	Abnormal behavior NOS
1	Aggression
1	Agitation
1	Alanine aminotransferase increased
6	Anemia NOS
1	Anemia NOS aggravated
2	Anorexia
1	Aphthous stomatitis
5	Arthralgia
2	Arthritis NOS
1	Aspartate aminotransferase increased
1	Asthenia
3	Back pain
3	Bone pain
1	Breast cancer invasive NOS
1	Bronchitis acute NOS
1	Cardiac failure congestive
1	Cardio-respiratory arrest
1	Cerebrovascular accident
1	Cholelithiasis
1	Cognitive disorder NEC
1	Conduction disorder NOS
1	Conversion disorder
2	Dehydration
9	Depression
3	Diarrhea NOS
1	Disorientation
2	Disturbance in attention
2	Dizziness
1	Drug ineffective
1	Drug intolerance NOS
1	Despond NOS
17	Fatigue
1	Gamma-glutamyltransferase increased
1	General nutrition disorder
1	Groin pain
2	Headache NOS
1	Herpes zoster
1	Hyperkalemia
1	Infection NOS

Inf/Ara-C First Line Discontinuations, continued

# Patients with each AE	Grade 3 or 4 AE
2	Insomnia
2	Jaundice NOS
3	Leukopenia NOS
1	Lung infiltration NOS
2	Malaise
1	Malignant neoplasm aggravated
1	Methicillin-resistant staphylococcal aureus
1	Mood alteration NOS
1	Mood disorder NOS
2	Mucosal inflammation NOS
1	Multi-organ failure
2	Muscle weakness NOS
7	Myalgia
1	Myocardial infarction
2	Nausea
2	Neck pain
1	Neurotoxicity NOS
3	Neutropenia
1	Pain in limb
3	Pain NOS
1	Panic disorder NOS
4	Paresthesia
1	Parotitis
1	Photopsia
1	Pleural effusion
1	Pneumonia aspiration
1	Pulmonary edema NOS
6	Pyrexia
1	Renal failure aggravated
2	Renal failure NOS
1	Respiratory failure (excluding neonatal)
2	Sepsis NOS
1	Speech disorder
1	Stomatitis
1	Suicidal ideation
8	Thrombocytopenia
1	Vitreous floaters
3	Weakness
1	Weight decreased
1	White blood cell count increased

3.4. Hematologic Adverse Effects

The following Table of grade 3 or 4 hematologic adverse effects is modified from the Applicant's Study Report.

Table 53: Newly occurring grade 3/4 hematologic toxicities (first-line treatment)

Toxicity	Gleevec N=551 (%)			IFN+Ara-C N=533 (%)		
	Grade 3	Grade 4	Grade 3/4	Grade 3	Grade 4	Grade 3/4
Anemia	15	2	17 (3.1)	22	1	23 (4.3)
Leukopenia	43	0	43 (7.8)	64	4	68 (12.8)*
Neutropenia	63	12	75 (13.6)	108	23	131 (24.6)**
Thrombocytopenia	38	1	39 (7.1)	84	3	87 (16.3)**
* p-value<0.01 (Fisher's Exact Test) ** p-value<0.001 (Fisher's Exact Test)						

3.5. Biochemical Adverse Effects

The following Table is modified from the Applicant's study report.

Table 54: Newly occurring grade 3/4 biochemical toxicities (first-line treatment)

	Gleevec N=551 (%)	IFN+Ara-C N=533 (%)
SGOT	17 (3.1)	22 (4.1)
SGPT	19 (3.4)	30 (5.6)
SGOT/SGPT	23 (4.2)	38 (7.1)
Total bilirubin	4 (0.7)	1 (0.2)
Alkaline phosphatase	1 (0.2)	4 (0.8)
Creatinine	0	2 (0.4)

4 Adequacy of Safety Testing

Gleevec safety has been evaluated for a median of 421 days in 551 patients as first line treatment for CML in chronic phase. The median duration of survival in these patients may be 6 years or more. Gleevec safety evaluation is adequate for marketing for this indication. But the Applicant should be required to submit annual safety updates on this trial.

5 Summary of Critical Safety Findings and Limitations of Data

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

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

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

VIII Dosing, Regimen, and Administration Issues

The protocol-specified starting dose of Gleevec was 400 mg per day, and 86% of all doses given were at the 400 mg dose level. Two percent (2%) of all doses were held, 9.5% of all doses were reduced, and 2% of all doses were increased above the recommended starting dose up to a maximum dose of 800 mg per day (see Tables 14 and 15). The approved dose is 400 mg for chronic phase after interferon and 600 mg for accelerated phase. Gleevec appears to be well tolerated at doses up to 800 mg, and there appears to be a wide therapeutic window, especially compared with cytotoxic agents.

IX Use in Special Populations

1 Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

1.1. Evaluation of Gender Effects on Efficacy

The Applicant did not find any gender effects on efficacy. The reviewers conducted our own analysis of gender effects on efficacy using the Applicant's submitted database. No gender effect is apparent on the primary efficacy endpoint of Time to Progression or on Time to Accelerated Phase or Blast Crisis.

Progression analyses by gender are summarized in the tables below.

Table 55: Effect of Gender on Time To Progression

Treatment Groups	Events	Censored	P Value Two-Sided	Median TTP
All Pts Gleevec	24	529	LR = <.00001	not reached
All Pts Inf+Ara-c	103	450	W = <.00001	not reached
Male Pts Gleevec	16	326	LR = < .0001	not reached
Male Pts Inf+Ara-c	70	240	W = < .0001	not reached
Female Pts Gleevec	8	203	LR = < .0001	not reached
Female Pts Inf+Ara-c	33	210	W = < .0001	not reached
Male Pts Gleevec	16	326	LR = .6054	not reached
Female Pts Gleevec	8	203	W = .4852	not reached

Table 56: Effect of Gender on Time to Accelerated Phase or Blast Crisis

Treatment Groups	Events	Censored	P Value Two-Sided	Median
All Pts Gleevec	.10	543	LR = < .0001	not reached
All Pts Inf+Ara-c	35	517	W = < . 0001	not reached
Male Pts Gleevec	8	334	LR = .0002	not reached
Male Patients Inf+Ara-c	24	285	W = .0003	not reached
Female Pts Gleevec	2	209	LR = .0090	not reached
Female Pts Inf+Ara-c	11	232	W = .0057	not reached
Male Pts Gleevec	8	304	LR = .2351	not reached
Female Pts Gleevec	2	209	W = .1154	not reached

Conclusions: Any effects of gender on progression were small compared with the effects of treatment.

1.2. Evaluation of Gender Effects on Safety

The reviewers conducted our own analysis of gender effect on safety using the Applicant's submitted database. The Applicant used the Preferred Terms for the adverse effects in their evaluation of adverse effects in the RCT and in their proposed labeling. For some unexplained reason the Applicant used Body Organ System in their evaluation of gender effects on safety. The FDA reviewers have used the Preferred Terms for evaluation of gender effect on safety. Both the FDA and the Applicant found a gender effect with certain adverse effects being more common in women. Minor differences can be resolved during labeling review.

Although gender analysis for safety is required, CDER has no regulations, policies, guidelines or criteria for what constitutes a gender effect on safety. The reviewers have used a Fisher's Exact Test P< 0.005 as the criterion for a gender difference in a specific adverse effect.

Using this criterion and ignoring adverse effects that can occur only in one gender, the following adverse effects appear to be more frequent in women: periorbital edema, edema NOS, peripheral edema, face edema, rigors, nausea neutropenia and headache.

There are no adverse effects that appear to be more frequent in men.

Table 57: Gender Comparison of Gleevec Adverse Effects with Chi Square P< 0.005

Adverse Events	# Males With AE N=341	# Females With AE N=210	%Male Pts With AE	% Female Pts with AE	ChiSq	P= 0.005	Fishers Exact P Value
Menorrhagia	0	11	0.0	5.2	19.63	7.88	.00002
Dysmenorrhoea	0	9	0.0	4.3	18.28	7.88	.0001
Periorbital edema	67	75	19.6	35.7	17.75	7.88	.00003
Rigors	14	24	4.1	11.4	12.14	7.88	.0015
Menstruation irregular	0	6	0.0	2.9	12.12	7.88	.0015
Oedema NOS	12	22	3.5	10.5	10.75	7.88	.0015
Nausea	127	107	37.2	51.0	10.21	7.88	.0018
Neutropenia	19	28	5.6	13.3	9.85	7.88	.0025
Oedema peripheral	41	46	12.0	21.9	9.79	7.88	.0025
Anemia NOS	11	19	3.2	9.0	9.71	7.88	.0058
Face edema	12	20	3.5	9.5	9.06	7.88	.0045
Headache NOS	82	75	24.0	35.7	8.49	7.88	.0035
Hot flushes NOS	3	10	0.9	4.8	8.32	7.88	.0065

Most oncology drugs are dosed based on body surface area or weight. The Gleevec dose is the same for all patients regardless of size. Women may have more adverse effects than men may, because they are smaller. As indicated in the following Table women are 15% smaller based on median body surface area and 17% smaller based on median weight.

To explore this hypothesis we removed the gender factor by comparing Gleevec safety in big women with small women. We compared the upper 25th percentile by weight with the lower 25th percentile. We also compared Gleevec safety in big men with small men using the same approach. The differences in median weight between big women and small women and between big men and small men were greater than the difference in median weight between men and women. We found no difference in the frequency of adverse effects either between big and small women or between big and small men.

Table 58: Gleevec Gender Dose, Duration, and Size

	Median Dose	Avg. Dose	Median Duration	Avg. Duration	Median BSA	Avg. BSA	Median WT	Avg. WT
Male	400	389	420	410	2.0	2.0	82	85
Female	400	380	422	412	1.7	1.8	68	73

The reason for the gender difference in safety is not apparent. We have asked our clinical pharmaceutical colleagues to determine if there is a pharmacokinetic explanation.

2 Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

2.1. Evaluation of Age Effects on Efficacy

The reviewers conducted our own analysis of age effects on efficacy using the Applicant's submitted database. Efficacy was compared between patients < 60 and patients ≥ 60 years of age. There is no apparent age effect on the primary efficacy endpoint of Time to Progression or on Time to Accelerated Phase or Blast Crisis. There is a suggestion that within the Gleevec treatment group that Gleevec may be more effective in patients < 60 years of age than in patients ≥ 60 years of age, but this is not conclusive. There is no apparent age difference in efficacy within the Alpha Interferon + Ara-C treatment group.

The Applicant did not find any age effects on efficacy.

Table 59: Effect of Age on Time to Progression

Treatment Groups	Events	Censored	P Value Two-Sided	Median TTP
All Pts Gleevec	24	529	LR = <.0001	not reached
All Pts Inf+Ara-c	103	450	W = <.0001	not reached
<Age 60 Gleevec	15	424	LR = < .0001	not reached
< Age 60 Inf+Ara-c	81	344	W = < .0001	not reached
≥ Age 60 Gleevec	9	105	LR = < .0010	not reached
≥ Age 60 Inf+Ara-c	22	106	W = < .0013	not reached
< Age 60 Gleevec	15	424	LR = .0538	not reached
≥ Age 60 Gleevec	9	105	W = .0419	not reached
< Age 60 Inf+Ara-c	81	344	LR = .6820	not reached
≥ Age 60 Inf+Ara-c	22	106	W = .6033	not reached

Table 60: Effects of Age on Time to Accelerated Phase or Blast Crisis

Treatment Groups	Events	Censored	P Value Two-Sided	Median TTP
All Pts Gleevec	24	529	LR = <.0001	not reached
All Pts Inf+Ara-c	103	450	W = <.0001	not reached
< Age 60 Gleevec	7	432	LR = .0001	not reached
< Age 60 Inf+Ara-c	27	397	W = .0001	not reached
≥ Age 60 Gleevec	3	111	LR = .1028	not reached
≥ Age 60 Inf+Ara-c	8	120	W = . 1508	not reached
< Age 60 Gleevec	7	432	LR = .4661	not reached
≥ Age 60 Gleevec	3	111	W = .3508	not reached
< Age 60 Inf+Ara-c	27	397	LR = .9603	not reached
≥ Age 60 Inf+Ara-c	8	120	W = .8997	not reached

2.2. Evaluation of Age Effects on Safety

The reviewers conducted our own analysis of age effect on safety using the Applicant's submitted database. The Applicant used the Preferred Terms for the adverse effects in their

evaluation of adverse effects in the RCT and in their proposed labeling. For some unexplained reason the Applicant used Body Organ System in their evaluation of age effects on safety. The FDA reviewers have used the Preferred Terms for evaluation of age effect on safety. Both the FDA and the Applicant found an age effect with certain adverse effects being more common in patients age ≥ 60 years. Minor differences can be resolved during labeling review.

Although age analysis for safety is required, CDER has no regulations, policies, guidelines or criteria for what constitutes an age effect. The reviewers have used a Fisher's Exact Test P< 0.005 as the criterion for an age difference in a specific adverse effect.

Using this criterion only eyelid edema is more frequent in-patients ≥ 60 years than in younger patients. Using a Chi Square P< 0.005 as the criterion, all of the adverse effects in the Table below are more frequent in patients ≥ 60 years of age than in younger patients.

Table 61: Age Comparison of Gleevec Adverse Effects with Chi Square P < 0.005

Adverse Events	# Pts <60 AE N=437	# Pts ≥60 AE N=114	%Pts <60 AE	% Pts ≥60 AE	ChiSq	P= 0.005	Fishers Exact P Value
Hematoma NOS	2	5	0.5	4.4	18.85	7.88	.0051
Hemorrhoids	4	7	0.9	6.1	15.56	7.88	.0021
Fungal infection NOS	1	4	0.2	3.5	11.35	7.88	.0073
Conjunctival hemorrhage	2	4	0.5	3.5	10.90	7.88	.0185
Fall	2	4	0.5	3.5	10.90	7.88	
Gout	2	4	0.5	3.5	10.90	7.88	
Eye discharge	3	4	0.7	3.5	10.60	7.88	.0364
Dry eye NOS	5	6	1.1	5.3	9.96	7.88	.0129
Face edema	18	14	4.1	12.3	9.54	7.88	.0248
Eyelid edema	29	18	6.6	15.8	8.91	7.88	.0039

2.3. Evaluation of Race Effects on Efficacy and Safety

We agree with the Applicant that there are insufficient numbers of patients in the non-Caucasian races to permit analyses.

3 Evaluation of Pediatric Program

4 Comments on Data Available or Needed in Other Populations

The long-term effects of Gleevec in CML patients prior to stem cell transplant (SCT) has not been studied. Since many eligible CML patients may eventually go on to SCT, information on the effects on safety and efficacy in this population would be useful.

X Conclusions and Recommendations

Conclusions

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

Recommendations

Gleevec should be granted Accelerated Approval, under CFR§314.510 Subpart H, for in the treatment of newly diagnosed adult Philadelphia chromosome-positive CML patients. The applicant should be required as a condition of approval under Subpart H to agree to provide interval follow-up safety and efficacy information on study 106 annually for six additional years.

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Gleevec First Line CML Indication

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