least one dose of trial medication. The efficacy analyzable population had originally consisted of all patients who received study drug for at least 3 weeks and who did not violate any inclusion criteria (except life expectancy > 6 months and at least one measurable site of disease that had not been embolised or irradiated).

*Reviewer comment : The requirement for a 3 week duration of treatment for inclusion in the efficacy analyzable (EA) population was removed but not included in a formal amendment.*

The primary efficacy endpoint was defined as best overall tumor response and was based on the ITT and efficacy analyzable populations. Patients with missing tumor response or who died or discontinued the trial before having the first post-baseline assessment were considered non-responders. Analyses were to be based on a 95% confidence interval for the response rate. For purposes of this submission, there is proof of efficacy if the lower limit of the confidence interval is at least 10%. Confidence interval calculations were also planned for the difference of response rates between treatment groups (normal approximation).

*Reviewer comment : Amendment #2 called for a change in details of tumor assessment so that Novartis would recalculate investigator assessments of response and specified that in the event of discrepancies, central Novartis calculations would be used for primary analyses and investigator evaluations would be used for 'sensitivity analyses', allowing a comparison between Novartis and investigator assessments.*

Secondary efficacy endpoints were to include: duration of response, time to onset of response, time to treatment failure (TTF) and overall survival.

Duration of response was defined as the time from onset of at least a PR (that was subsequently confirmed) to the time of first tumor assessment noting PD. If a determination of PD was preceded by an assessment of UNK, it is the time of UNK that was used as the end time of response.

*Reviewer comment : According to the SWOG criteria utilized in the protocol, an assessment of unknown (UNK) refers to an assessment where progression has not been documented and one or more measurable or evaluable sites were not assessed.(See Appendix XI. A)*

Time to onset of response has been analyzed, by the sponsor, as a time to event endpoint. The starting date is the date of first dose. For patients who responded, the end date is date of the first tumor assessment that was subsequently confirmed as at least a PR. Patients who did not have a confirmed PR or CR were censored at the time of their last progression-free tumor assessment.

TTF has been analyzed by the sponsor as a time to event endpoint. The starting date is the date of first dose. The end date is the earliest date of any progression, death due to any cause, or discontinuation from the trial for any reason other than "condition no longer requires therapy." If a determination of PD was preceded by an assessment of UNK, it is the date of UNK that is used as the end date.

*Reviewer comment : Response duration replaced time to progression as a secondary endpoint for this submission. This change was not included in a protocol amendment.*

## 2. Trial Results

### Study Conduct

### Informed Consent and Treatment Assignment

Informed consent was obtained before performing any procedure to determine patient eligibility. A nine-digit patient identification number was then assigned, with the first four digits identifying the center and the last five digits identifying the sequence in which the patients entered the study.

### Randomization

Novartis performed central randomization with a 1:1 randomization scheme produced by Novartis Drug Supply Management. Once a patient passed the screening period and was confirmed eligible for the trial by the Principal Investigator at the respective study center, the randomization number and the matching treatment group (dose) were communicated to the investigator by fax. After randomization, the treatment allocation was not blinded for Novartis, the investigator, nor the patient. Randomization was not center dependent.

### Blinding

Not applicable

### Central Reviewed Pathology

A central pathology review has been conducted by ——— ——— The submitted report is dated 8/15/01 and states that "at that time, 124 of the 147 cases had been reviewed (84%) with original pathology materials or unstained slides still being gathered from study centers outside ——— ..123 of the 124 cases show morphologic features typical of GI stromal sarcoma and the diagnosis has been confirmed in all of these cases by convincing KIT (CD117) immunopositivity...Only one case to date (ref#502-69) was deemed ineligible on the basis of pathology review. This was a gastric mass which morphologically differed from GIST, stained negatively for KIT but was positive for keratin and epithelial membrane antigen, and which was reclassified as monophasic synovial sarcoma." This patient, initially randomized to a dose of 600 mg daily,was discontinued from the study due to progressive disease prior to reclassification by the central pathologist.

An update of the central pathology review was provided on 11/08/01. According to the sponsor, ten additional cases have been reviewed since the pathology report was issued for a total of 134 reviewed. Of these, one additional patient was found not to have GIST (one additional since the report was released). Therefore, 13 cases are pending central review. The additional patient reclassified as having a non-GIST tumor was patient 502/121; initially randomized to a dose of

400 mg daily. This patient was also discontinued due to progressive disease prior to reclassification.
*Reviewer comment : Patient 502/121 was initially diagnosed with GIST in 1997. However, a biopsy of tumor tissue at recurrence in 2001 was apparently negative for KIT. An updated report to be submitted once review of the 13 pending cases is complete will be requested as a component of the phase 4 commitments.*

**Protocol Violations**

The sponsor states that the only patient who withdrew from the trial for a protocol violation (patient 502/121) discontinued due to a requirement for concurrent therapy. This patient was not excluded from the efficacy analyzable population.

*Reviewer comment : According to the patient narrative submitted by the sponsor (page 15 of the ISS- Post-text supplement #3), this patient had been hospitalized on 4/27/01 for grade 3 anemia, gastrointestinal bleeding, melena and hematemesis. Treatment included vitamin K, erythrocyte transfusion, opioid analgesics and diuretics. An endoscopy performed on 4/30/01 revealed no evidence of bleeding. Imatinib was discontinued on 5/3/01 in order to allow a course of mid abdominal radiation in an attempt to control intra-abdominal bleeding. This patient expired on 5/08/01.*

The sponsor states that patient 502/069 was found not to have GIST after generation of the tables produced for the sponsor's study report. (see central pathology review section above)

Patient (502/105) initially randomized to the 400 mg dose group was found to have no measurable lesions and declared a screening failure. The patient never received study medication and no data for this patient was provided for the clinical database. This patient was not included in the total N for efficacy analysis.

**Enrollment, Demographics, Baseline Characteristics**

**Enrollment by Study Center**

A total of 147 patients were enrolled at 3 U.S. centers and one in Finland. The largest center for enrollment was the Dana Farber Cancer Center in Boston. Table 4 provides a summary of enrollment by center and dose.

**Table 4: Enrollment by Center and Dose**

| Center | Number (%) | | |
|---|---|---|---|
| | 400 mg | 600 mg | All doses |
| Dana Farber Cancer Institute, Boston | 37 | 44 | 81 (55.1%) |
| Fox Chase Cancer Center, Philadelphia | 14 | 14 | 28 (19%) |
| Oregon Health Sciences University, Portland | 15 | 12 | 27 (18.4%) |
| Helsinki University Central Hospital, Finland | 7 | 4 | 11 (7.5%) |
| Total | 73 | 74 | 147 (100.0%) |

**Baseline Demographics**

Table 5 (Sponsor Table 3-1 of ISS) presents demographic information by dose assigned and pooled across doses. Slightly more patients were male. Most patients were Caucasian and most had an ECOG performance status of 0 or 1. Twenty-nine percent of patients were older than 60 years and 10% were older than 70 years.

**Table 5: Demographic Variables**

| Demographic variable | 400 mg (N=73) | 600 mg (N=74) | All doses (N=147) |
|---|---|---|---|
| **Age (years)** | | | |
| N | 73 | 74 | 147 |
| Mean | 56.8 | 52.2 | 54.4 |
| SD | 12.90 | 11.12 | 12.20 |
| Median | 58 | 52 | 54 |
| Min - max | 26 - 83 | 18 – 79 | 18 - 83 |
| **Sex - n (%)** | | | |
| Male | 44 (60.3) | 39 (52.7) | 83 (56.5) |
| Female | 29 (39.7) | 35 (47.3) | 64 (43.5) |
| **Race - n (%)** | | | |
| Caucasian | 69 (94.5) | 67 (90.5) | 136 (92.5) |
| Black | 1 (1.4) | 4 (5.4) | 5 (3.4) |
| Oriental | 2 (2.7) | 2 (2.7) | 4 (2.7) |
| Other | 1 (1.4) | 1 (1.4) | 2 (1.4) |
| **ECOG status - n (%)** | | | |
| Grade 0 | 28 (38.4) | 34 (45.9) | 62 (42.2) |
| Grade 1 | 28 (38.4) | 29 (39.2) | 57 (38.8) |
| Grade 2 | 16 (21.9) | 11 (14.9) | 27 (18.4) |
| Grade 3 | 1 (1.4) | 0 | 1 (0.7) |
| Grade 4 | 0 | 0 | 0 |

(Sponsor Table 3-1 of ISS)

**Disease Characteristics of the Patient Population**

The most common sites for the primary tumor were the small intestine and stomach. Approximately 90% of patients had recurrent disease at study entry. Table 6 summarizes common sites of primary tumor.

**Table 6 : Primary Disease Sites**

| Site of primary | Number (%) |
|---|---|
| Stomach | 50 (34%) |
| Small intestine | 72 (49%) |
| Colon | 11 (7.5%) |

Table 7 summarizes prior therapy in the patient population. Almost all patients had undergone surgery as treatment for GIST. Approximately 50% had received prior chemotherapy. No patient achieved CR or PR on prior systemic therapy. There were no major differences in the distribution of prior therapy between the two dosing arms.

**Table 7 : Prior Therapy**

| Prior Treatment For GIST | Number (%) | | |
|---|---|---|---|
| | 400 mg | 600 mg | Total (n=147) |
| Chemotherapy | 41 | 34 | 75 (51%) |
| Radiotherapy | 9 | 13 | 22 (15%) |
| Surgery | 71 | 73 | 144 (98%) |

**Efficacy Results - Sponsor's Assessment**

The best (confirmed) tumor responses observed by the cut-off date for this interim analysis were calculated by Novartis based on SWOG response criteria (See protocol summary and Appendix). Patients were graded as 'not evaluable' for best response if they had only one or no assessment of tumor response after baseline, unless this assessment was a PD or the patient discontinued for PD, in which case the patient had a best response equal to PD. Patients were graded UNK if they had at least two assessments after baseline but did not qualify for another category of best response, for example, if they had one assessment of SD with a second assessment of UNK disease status.

Overall, 40% (59/147) of patients achieved a confirmed PR according to the sponsor (Table 8, sponsor table 2 of ISE). The corresponding 95% confidence interval for response rate is (32.1, 48.5), and because the lower limit is above 10%, it is the sponsor's assessment that it fulfills the efficacy criterion established for this study. No patient has achieved a CR as of this submission. The sponsor states that the trend for any dose relationship to response is not statistically significant based on a 95% confidence interval for the difference in response rates (400 mg minus 600 mg) of (-22.1%, 9.6%). The response rates for the individual dose groups, according

to the sponsor, are 37% with 95% confidence interval of (26%, 49%) for 400 mg and 43% with 95% confidence interval of (32%, 55%) for 600 mg.

**Table 8 : Best Tumor Response, sponsor assessment**

| | All doses (N=147) 400 mg n=73 600 mg n=74 |
|---|---|
| **Best response** | **n (%)** |
| **Complete response** | 0 |
| **Partial response** | 59 (40.1) |
| **Stable disease** | 61 (41.5) |
| **Progressive disease** | 18 (12.2) |
| **Not evaluable** | 7 (4.8) |
| **Unknown** | 2 (1.4) |

(Sponsor Table 2, ISE)

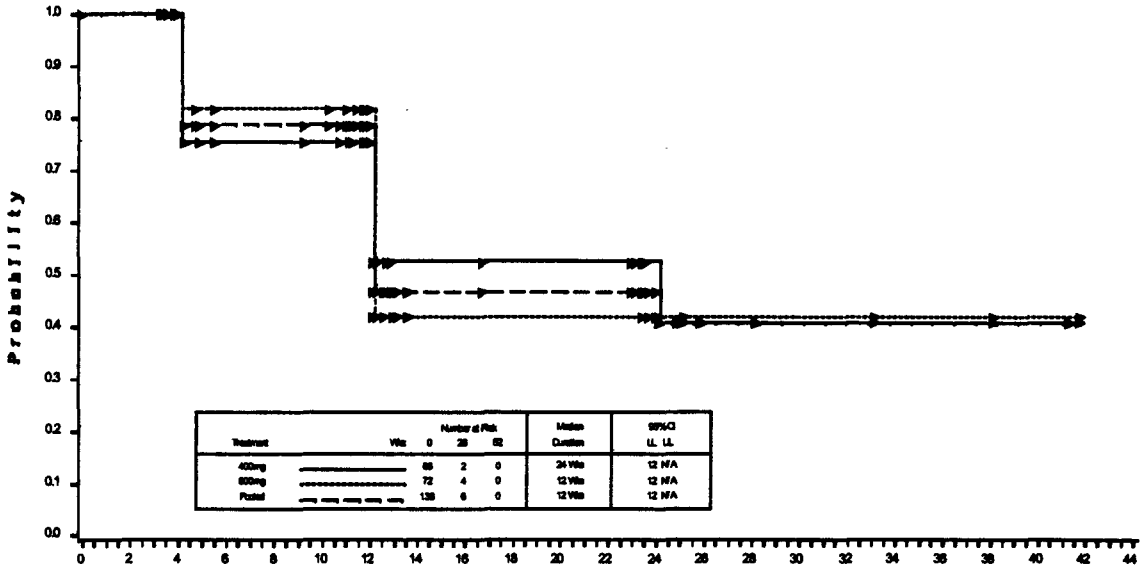
**Secondary Efficacy Results**

Time to onset of response, duration of response, TTF and overall survival were to be evaluated as secondary efficacy parameters.

**Time to onset of response**

The Kaplan-Meier plots for time to onset of response are presented in Figure 1 of the sponsor's ISE and were based on Novartis estimates with "interval censoring." According to the sponsor, median time to onset of response was 12 weeks for the entire study population. Kaplan-Meier curves generated for each dose group crossed and no difference between treatment groups was identified.

**Sponsor Figure 1(ISE) Kaplan-Meier estimate of time to response**




**Weeks post first dose**

Note: Plot is based on the Novartis assessment, with interval censoring
Hazard ratio: 1.080, Log rank test p=0.8830

*"At risk at 26 weeks" in sponsor's figure 1 refers to number of patients with a time to onset of response greater than 26 weeks.*

No major difference in time to onset of response was observed using the response evaluations from Novartis versus the response evaluations of the investigators.

This analysis is based on the full TRT population and not only on patients with a confirmed response. Responders are counted at their first PR assessment that was later confirmed. Non-responders, including those patients whose last assessment was an unconfirmed PR, were censored at the date of their last progression-free tumor assessment.

*Reviewer comment : When the FDA could not reproduce these analyses, the sponsor was queried for details on their methodology. Their response indicates that actual dates of onset of response were changed to fit the scheduled dates of tumor assessment. According to sponsor correspondence 11/28/01, the procedure for "interval censoring" and calculating onset of response was given according to the following : "The column "Sched. visit of onset of response" in listing 9.1-9a gives the interval-censored onset of response, presenting this as study day (e.g.m02w1d1) and as number of days since first dose of study medication. Tumor assessments had been scheduled at days 29, 85, 169 and 379 (plus assessments above year one, which do not yet exist). The values presented in this column have been produced by applying a format to the variable ONS_DAYS. This format merged all numbers between 14 and (29+14) into 29, 29+15 to 85+14 into 85, 85+15 to 169+14 into 169, 169+15 to 379+14 into 379, in order to find the next scheduled time of tumor assessment." In other words, dates of onset of response were changed to fit the scheduled dates. (For example, if a patient had a visit at day 185, this was*

*reclassified as day 379 for this interval-censored analysis). Analyses based on such adjustments cannot be justified. Such "adjustments" were also made to dates used to determine time to treatment failure, and duration of response in analyses where the sponsor used "interval censoring." Comparative results between dose arms are closer using the sponsor's "interval-censored" data than using the sponsor's "no interval censoring" data.*

*It should be emphasized that this analysis included the entire study population, and not only patients with a confirmed response.*

*In addition, the FDA could not reproduce the p-value associated with a hazard ratio of 1.080 as presented by the sponsor. For an estimate of the hazard ratio (600 mg/400 mg) of 1.080, a p-value of 0.8830 is consistent with a total number of events of about 14-15 (not 59 events). An FDA analysis using the sponsor's interval censored date of onset of response and censoring all non-responders at the date of last evaluation led to an estimate of the hazard ratio of 1.080 with a p-value of 0.7688 (consistent with 59 events).*

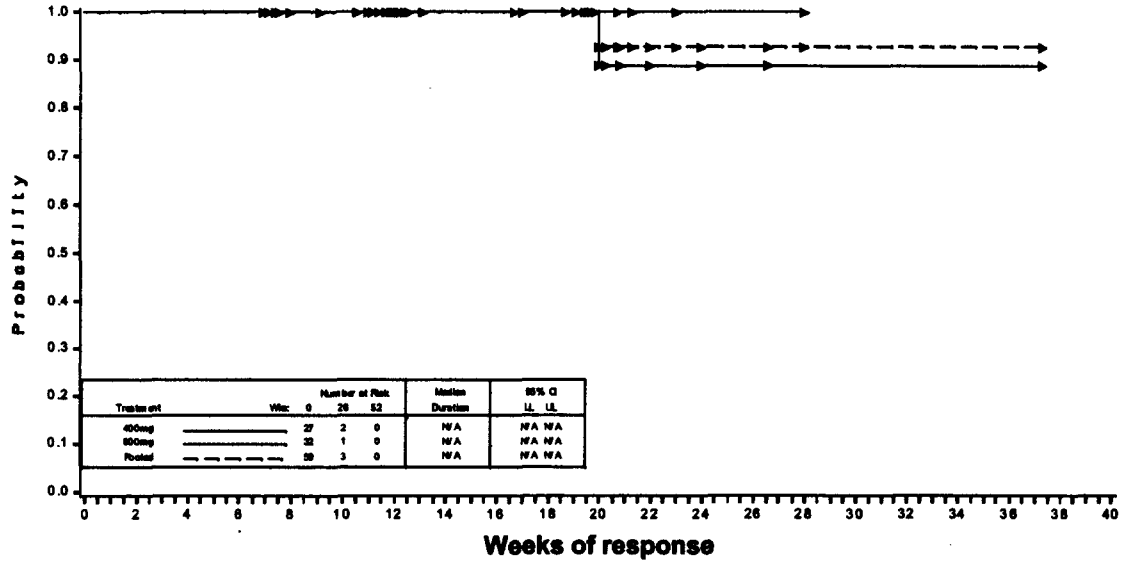
*Differences in estimates of median time to onset of response from roughly 12 weeks to roughly 24 weeks are misleading. There are very few observations between 12 and 24 weeks ( due to the visit schedule). In an FDA analysis, the estimate of the probability of a time to onset of response of at most 95 days is approximately 0.47 for the 400 mg dose group and approximately 0.52 for the 600 mg dose group*

*For those patients who progressed without responding, the sponsor's analysis approach to censor the time to onset of response at the time of their last progression-free evaluation is inappropriate. This treats such patients analogous to patients who neither responded nor progressed. A patient whose best response is progression and had their last tumor assessment at day 85 and a patient who has not responded nor progressed by day 85 and goes off study are both censored at 85 days. If the purpose is to regard someone who has progressed before responding as never being able to be classified as a responder, then their time to onset of response is infinite (unbounded). If the purpose is to determine the time to onset of response regardless of whether a patient had earlier progressed, then the time to onset of response for those patients who progressed without responding should be censored at the time of last evaluation.*

**Duration of response**

Duration of response is displayed in Figure 2. The duration of response observed thus far (Novartis assessment of response, no interval censoring) ranged from seven to 38 weeks.

**Sponsor Figure 2 (ISE) Kaplan-Meier estimates of duration of response**




Note: Plot is based on the Novartis assessment

Based on radiographic analyses of response, no major difference was observed between the results of duration of response evaluations performed by Novartis and those performed by investigators.

Only one out of the 59 patients who achieved a confirmed PR has progressed so far based on the guidelines used for the Novartis assessment of response. The investigator differed with Novartis in this assessment and graded the patient as being in a continuous state of PR. This patient (501/10, in the 400 mg dose group) had an initial reduction of tumor size from 1130 $cm^2$ to 231 $cm^2$ (80%, PR) followed by an increase of more than 10 $cm^2$ to 298 $cm^2$ (technically meeting criteria for PD as set forth in the protocol). Assessments following this PD evaluation demonstrated tumor shrinkage (latest tumor assessment as of this interim report: 220 $cm^2$), leading the investigator to consider this patient in continuous PR.

Based on the response assessments performed by the investigators, none of the responders have progressed so far.

Two responders discontinued the trial, while the remaining 57 sponsor assessed responders are continuing on the trial.

*Reviewer comment : One patient with a response discontinued the trial due to elevated transaminases. The other discontinued due to the development of interstitial lung disease.*

None of the 118 patients who experienced a >25% reduction in tumor size during at least one tumor evaluation were considered by the investigators to have developed progressive disease, although 10 of these patients did have an increase in tumor size meeting criteria for PD. However, it was reportedly the opinion of the investigators and radiologists that these increases in tumor size were not a consequence of tumor growth but secondary to either intra-tumoral bleeding or edema, or were otherwise insignificant when taking the total tumor burden into

consideration. Consequently eight of these patients continue treatment on study. Two of the ten patients are off study (one discontinued due to withdrawal of consent and one patient died from cardiac arrest).

*Reviewer comment : Duration of response data are premature. Many patients who responded are still on study at the time of the interim report. Many patients who had a partial response at their most recent tumor assessment had this assessment 2 to 5 months prior to the evaluation cutoff date for this sNDA.*

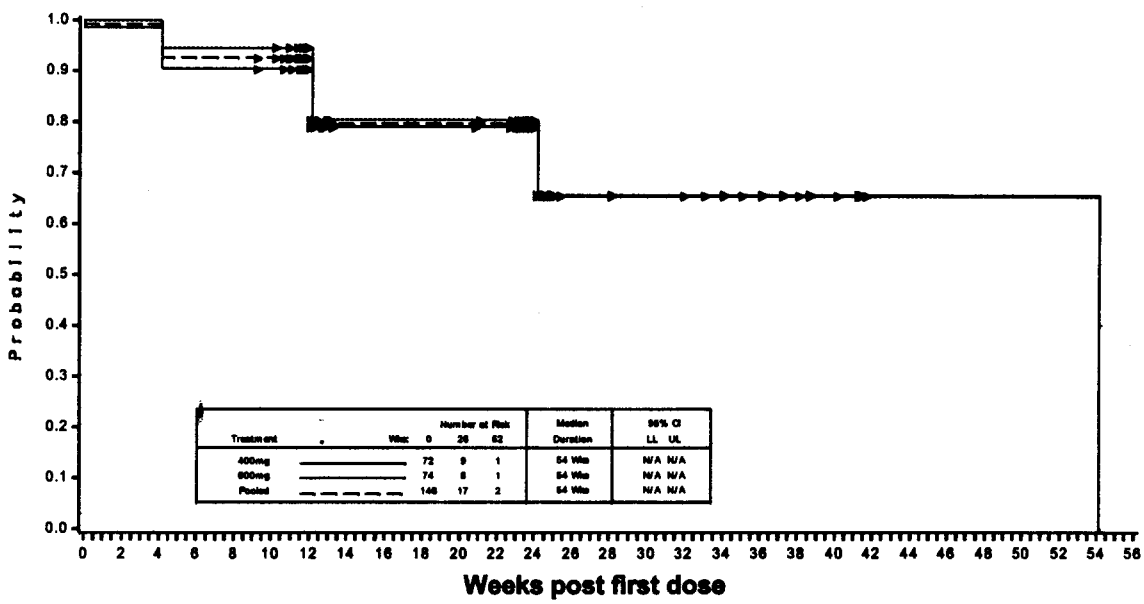
*The sponsor provides a discussion of patients with reductions in tumor volume that do not meet criteria for partial response (reductions <50% in tumor volume). The FDA does not regard these as contributing to the surrogate endpoint of response, which is defined by those with a complete or partial response.*

**Time to treatment failure**

The Kaplan-Meier estimate of patients who were free from treatment failure at 12 weeks was 80% and this estimate was 66% at 24 weeks. Without interval-censoring, the respective estimates were 81% and 67%, respectively. Only 22 of 147 patients were on the trial more than 25 weeks (as of this interim report), thus Kaplan-Meier estimates after 24 weeks are hard to interpret. A difference between dose groups could not be observed.

Kaplan-Meier plots that estimate the TTF are presented in Figure 3.

**Sponsor Figure 3 (ISE) Kaplan-Meier estimates of time to treatment failure**




Note: Plot is based on the Novartis assessment, with interval censoring
Hazard ratio: 0.93, Log rank test p=0.8081

*Reviewer comment : The time from when the first patient was entered into the trial (July 6, 2000) to the time of last evaluation of any patient for any analysis (July 10, 2001) is just under 53 weeks. Yet, two patients were given times to treatment failure of 54 weeks by the sponsor (these patients had entered the trial on 7/06/01 and 11/02/01). An inquiry was sent to the sponsor to*

*explain this discrepancy. The sponsor's response (correspondence dated 11-07-01) was "Discrepancy between clinical study report and TTF timelines: The designation [sic] of two treatment failures at week 54 are based on interval censoring. Tumor assessment [sic] for these patients were scheduled according to the visit schedule in the protocol. However, the tumor assessment occurred prior to the actual scheduled tumor assessment, and the data was projected to the next visit scheduled which was at week 54 (379 days, according to the protocol)." As discussed above, "adjustments" such as the ones described here are not justifiable.*

*Time to treatment failure is a composite endpoint. Here, it is an endpoint which includes elements of safety as well as efficacy.*

Table 9 (Sponsor Table 4 of ISE) summarizes treatment failures based on the Novartis assessment. Patients were considered disease related treatment failures if they had an assessment of progressive disease, if they discontinued due to unsatisfactory therapeutic effect or if they died from progression of disease.

**Table 9 : Treatment Failures, Sponsor Assessment**

| Treatment failures | Reason | All doses (N=147) n (%) |
|---|---|---|
| **Disease related** | Total | 30 (20.4) |
| | Death (any cause) | 8 (5.4) |
| **Other (all discontinued)** | Total | 8 (5.4) |
| | AE | 5 (3.4) |
| | Abnormal laboratory | 1 (0.7) |
| | Death due to unrelated AE | 2 (1.4) |
| | Consent withdrawal | 0 |
| **Total** | | 38 (25.8) |

(Sponsor Table 4, ISE)

**Overall survival**

Overall survival was not analyzed due to the small number of deaths observed thus far and the relatively short period that has elapsed since the recruitment of the entire study population into the trial.

Ten patients died during the trial or during follow-up. The time to death since the start of treatment ranged from 5.3 to 35.7 weeks in the entire population. Six deaths were attributed to disease progression. For the four patients whose deaths were not attributed to disease progression, the causes were listed as probable pulmonary embolism, respiratory failure, cerebrovascular accident and cardiac arrest, respectively.

Two additional deaths were reported as SAEs but are not captured in the current interim analyses. Both patients were discontinued from the study before expiring for reasons other than PD. However, both deaths occurred within 30 days of stopping treatment.

**Other Topics - $^{18}$FDG-PET Scanning**

$^{18}$Fluoro-deoxyglucose ($^{18}$FDG) Positron Emission Tomography (PET) scanning was performed to assess possible changes in the metabolic profile of the tumors and in order to compare this imaging technique with standard computer tomography (CT) imaging for monitoring tumor responses in study patients. CT scanning and attenuated-corrected 2-D whole body $^{18}$FDG-PET were performed in 25 consenting patients in center 501. Sites of disease defined by CT scan at baseline correlated with areas of abnormality on $^{18}$FDG-PET. However, $^{18}$FDG-PET showed additional sites of disease. Following the initiation of Gleevec™ therapy, 80% of the patients (20/25) demonstrated a response based on qualitative evaluation of the PET images.

*Reviewer comment : The statement that 'FDG-PET showed additional sites of disease' must be read with caution. FDG-PET is a functional, not an anatomic assessment. Sites of abnormal uptake assessed by FDG-PET and not detected by CT scan or MRI may represent processes separate from tumor activity. Specific criteria for how response was evaluated by PET are not provided; it is stated that this was a qualitative evaluation.*

A decrease in the standard uptake value (SUV) and the tumor to background ratio (TBR) could be observed as early as 24 hours following the administration of a single dose of Gleevec™. This early response was sustained and continued to improve up to seven months following initiation of therapy. With the exception of one patient who demonstrated a repeated hyperinsulinemic state, the qualitative evaluation of response to treatment was confirmed by TBR measurements.

For patients with SD or PD, concordant findings between $^{18}$FDG-PET and the bi-dimensional measurements made from CT images were seen in all but one patient who responded by PET but did not show a decrease in CT measurements. This was attributed to an intra-tumoral hemorrhage.

Lack of a metabolic response to $^{18}$FDG-PET was noted in 5/25 patients, one of whom exhibited primary resistance to the study drug and four of whom demonstrated either SD or PD by morphologic criteria. Six patients remained stable or progressed on Gleevec™ therapy based on CT scanning criteria (Reference 7, Appendix 4.1). The study findings are summarized in Table 10 (Sponsor Table 6 of ISE).

**Table 10 : Summary of 18FDG-PET Findings in 25 Study Patients from Center 501**

(Sponsor Table 6 of ISE)

| CT Scan | TBR[1] | PET | N (%) | Outcome |
|---|---|---|---|---|
| Decreased | Decreased | Complete response | 19 (76) | Continuing therapy |
| Stable | Stable | Stable | 1 (4) | Continuing therapy |
| Stable | Mild decrease | Partial response | 1(4) | Continuing therapy |
| Increased[2] | Decreasing | Complete response | 1(4) | Continuing therapy |
| Increased | Increased | Progression | 1(4) | Off study |
| Increased | Decreased[3] | Progression | 1(4) | Off study |
| Increased | Mild decrease | Partial response | 1(4) | Off study |

[1] TBR =Tumor-to-background ratio
[2] Possible intra-tumoral hemorrhage
[3] Hyperinsulinemic patient, possible false negative

*Reviewer comments : Column 2 (TBR) refers to tumor-to-background ratio as measured by PET imaging. Column 3 (PET) refers to assessment of response using PET measurements. It is important to note that FDG-PET was studied in a small number of patients. Of the 19 patients*

*with a decrease in tumor size on CT and a response on PET, 16 patients actually had an assessment of PR as the assessment of best objective response . No data is presented regarding any relationship between findings on PET and blood concentrations of Gleevec™.*

**FDA Analysis**

Baseline and best response radiology studies for responders were requested by the FDA in a communication to the sponsor forwarded 7/12/01. Radiology studies obtained at baseline and at best response for 90 patients were submitted by the sponsor and reviewed by the medical officers Ramzi Dagher and Martin Cohen. At the time of sNDA submission, it was apparent that the sponsor was claiming a confirmed partial response in 59 patients. The FDA requested a clarification of why radiologic studies were submitted for more patients than the sponsor was claiming responses for, and the sponsor explained that radiology studies had been submitted for patients with an unconfirmed response as well as patients with a confirmed partial response according to the sponsor's assessment. Table 11 summarizes the sponsor's assessment for the 90 patients for whom radiologic studies were submitted.

**Table 11 : Tumor Response by Sponsor for Submitted Scans**

| | Number of Patients | | |
|---|---|---|---|
| **Best Confirmed Response** | **400 mg** | **600 mg** | **Total** |
| Confirmed Partial Response | 27 | 32 | 59 |
| Unconfirmed Partial Response: | 16 | 15 | 31 |

Using SWOG criteria as described in the protocol and utilized by the sponsor, DODP/CDER medical officers reviewed baseline and best response radiologic studies for all 90 patients whose radiology studies were submitted. These included the 59 patients for whom a confirmed PR was claimed by the sponsor according to SWOG criteria. In 40/59 patients, the reviewers agreed with the sponsor's assessment of a confirmed partial response. The remaining 19 cases were reviewed by a consultant radiologist, Dr. Ronnelle Dubrow of MDACC. The FDA's final assessment was that a confirmed partial response could be documented in 56 patients corresponding to a response rate of 38%. Table 12 summarizes response rate by dose per FDA analysis.

**Table 12 : Tumor Response by Dose per FDA analysis**

| **Total Patients N** | | **Confirmed PR N (%)** | **95% Confidence Interval** |
|---|---|---|---|
| 400 mg daily | 73 | 24 (33%) | 22%, 45% |
| 600 mg daily | 74 | 32 (43%) | 32%, 55% |
| Total | 147 | 56 (38%) | 30%, 46% |

The 95% confidence interval for the tumor response rate was (22%, 45%) for the 400 mg dose group and (32%, 55%) for the 600 mg dose group. These confidence intervals lie entirely above 10%. The 95% confidence interval associated with the overall tumor response rate of 38% is

(30%, 46%). The 95% confidence interval for the difference in tumor response rates (400 mg – 600 mg) is (-26%, 5%).

In 3 patients, the FDA medical reviewers and the FDA's consultant radiologist disagreed with the sponsor's assessment of a confirmed partial response. These were patients 501/62, 501/87, and 503/0058, and the FDA's assessment for response in these patients was stable disease. All three patients were randomized to a dose of 400 mg daily. *In an electronic communication dated 12/07/01, the sponsor indicated that they have reviewed the CT scans of these 3 patients with an outside radiologist and they do not dispute the FDA assessment.*

Of the 56 patients with a confirmed partial response, there were 29 males and 27 females. The response rates in the male and female populations are (29/83) 35% and (27/64) 42% respectively. There appears to be no significant difference in response rates between males and females, but the limited number of patients precludes a formal analysis.

The 56 patients with a confirmed partial response ranged in age from 28 years to 79 years with a mean of 55 years, compared to a mean age of 54.4 years in the total study population of 147 patients. There were 11 patients older than 65 years who had a partial response. Although the response rate in patients older than 65 years (11/23 or 48%) appears to be slightly higher than that in patients 65 years or younger (45/124 or 36%), the small number of patients older than 65 years in the study population precludes any conclusion in this regard.

FDA analysis indicates a range of response duration from 7 to 38 weeks. At the cutoff date for the study report, 55 of 56 patients with a confirmed partial response had a maintained, ongoing PR. Only one of 56 patients had documented progression by the cut-off date. This patient with the lone uncensored response duration actually remained on treatment despite evidence of disease progression and on subsequent imaging had, once again, evidence of a partial response. For this patient the time from first diagnosis of a response to the last successive diagnosis of a response was 142 days. The time from first assessment of a response to the last tumor evaluation was 198 days.

The 55 censored response durations in days are summarized in the stem-and-leaf plot below (Reviewer Figure 1).

**Reviewer Figure 1. Stem-and-leaf Plot of Censored Response Durations (Stem unit = 10 days and leaf unit = 1 day ; for example 5 2 in the second row refers to 50 days + 2 days =52 days duration for one patient)**

```
 4 9
 5 24667
 6 6
 7 017778
 8 1333444444478
 9 015
10 4
11 2
12 02
13 3334777
14 0003577
15 5
16 5
17
18 19
19
20 19
21
22 1
23
24
25
26 6
```

These censored response durations were skewed to the right, with a median of 91 days (13 weeks), a range from 49 days to 266 days (7 weeks to 38 weeks) and an interquartile range from the 25$^{th}$ percentile of 81 days (11-12 weeks) to the 75$^{th}$ percentile of 140 days (20 weeks).

The sponsor presented a time to response analysis in the sNDA and the FDA review team did not find that the methodology used for this analysis was appropriate. Given the relatively short duration of followup in this study, it is possible that not all of the responses have been documented and the median time to onset of response analyzed at this early point in followup could yield inaccurate results. For this reason, the data for time to response of each confirmed responder in the study (at the time of data cut-off) has been described below in a stem-and-leaf plot.

**Reviewer Figure 2. Stem-and-leaf Plot of Time Interval to Response for Each Confirmed Responder**
**(Stem unit = 10 days and leaf unit = 1 day ; for example 2 4 in the first row refers to 20 + 4 days time interval for one patient)**

```
 2 44666677788999999
 3 0112345
 4 0
 5 27889
 6 028
 7 5669
 8 00244555679
 9 014557
10
11
12
13
14
15
16 69
```

The majority of patients with a confirmed partial response had onset of response by day 89 after starting treatment with imatinib.

### D. Efficacy Conclusions

The efficacy database for the GIST indication consists of a single open label phase 2 trial of imatinib in 147 patients with metastatic and/or recurrent GIST with 73 patients randomized to 400 mg daily and 74 patients randomized to 600 mg daily. An overall objective partial response rate of 38% (FDA analysis, pooled for both dose levels) was demonstrated at the study cutoff date with an ongoing response in 55 of 56 patients with a confirmed PR. Median response duration cannot be determined yet because of limited followup. FDA review of the radiologic studies utilized to determine the primary endpoint of best overall objective response allowed for independent substantiation of the results.

Subpart H of the NDA regulations allows accelerated approval for serious or life-threatening diseases. For indications where the new drug appears to provide benefit over available therapy, accelerated approval may be granted on the basis of a surrogate endpoint that is reasonably likely to predict clinical benefit. After approval, the sponsor is required to perform a post-marketing study to demonstrate that treatment is associated with clinical benefit. If the studies fail to demonstrate clinical benefit or if the sponsor does not show "due diligence", the drug may be removed from the market.

For this sNDA, objective response rate is considered a surrogate endpoint. In the disease setting of malignant, inoperable and/or metastatic GIST, where standard chemotherapy is expected to yield a response rate no more than 0-5%, an objective tumor response of at least a PR (50% or greater reduction in overall tumor size as measured bidimensionally) is considered reasonably likely to predict benefit. Radiation therapy has not been demonstrated to be of any benefit and has not been associated with response in this disease. The pooled response rate of 38% observed in the study (33% for the 400 mg dose group and 43% for the 600 mg dose group) that was the basis for this sNDA is much higher than that associated with available therapy, and justifies consideration of accelerated approval of imatinib in patients with metastatic and/or inoperable malignant GIST.

Efficacy results do not support full approval for this indication. As outlined above, the relatively short duration from study initiation to the cutoff date does not allow for an adequate evaluation of duration of response. Highly durable responses may reflect real clinical benefit in this patient population with essentially no effective therapy available to them.

## VII. Integrated Review of Safety

This section will include safety analyses performed by the sponsor and by the FDA. Similarities and discrepancies of the two analyses will be indicated and discussed, when pertinent.

### A. Sponsor's Conclusions

Gleevec™ (imatinib mesylate) has been tested in a clinical trial (B2222) involving 147 patients with metastatic or recurrent GIST, all of whom were included in the safety population.

In B2222, patients were randomized between imatinib 400 mg (73 patients) and 600 mg (74 patients) daily. The patient population included slightly more men than women (56.5% versus 43.5%). Less than 8% of patients were non-Caucasian. The median age of study patients was 54 years (range 18-83). Eighty-one percent of patients were ECOG performance status 0 or 1.

In study B2222, the most frequently reported individual AE (reported as having a possible relationship to study drug) was mild to moderate nausea in 51% of patients, sometimes accompanied by vomiting and abdominal pain. Diarrhea was the second most common AE, followed by periorbital edema, muscle cramps and fatigue. Headache and skin rash were other AEs that were reported in 25% of GIST patients. AEs were generally mild to moderate (Grade1/2) in severity, with Grade 3/4 episodes generally reported in $\leq$5% of patients for individual AEs. Treatment was discontinued for drug-related AEs in only four of the 147 patients (3%) of patients. There were only minor differences in the pattern and incidence of

the most commonly reported AEs between the GIST and CML patient populations. No clear relationship to dose was apparent though diarrhea, edema, muscle cramps, headache and dermatitis were reported somewhat more frequently in patients treated at 600 mg daily.

In study B2222, ten patients had died by data cut-off for the study report. None of these deaths was suspected to be related to study medication.

The incidence of grade 3/4 myelosuppression was lower in GIST patients compared to that reported in the leukemia studies. In data submitted in the NDA in February 2001 for the registration in CML, grade 3 neutropenia and thrombocytopenia were reported in 24% and 16% of patients with chronic phase CML, respectively. For the GIST patients in B2222, the corresponding figures were 4% and 0.7%, respectively. Grade 4 episodes of neutropenia and thrombocytopenia were 8% and 0.4% vs 3% and 0% for CML and GIST patients, respectively. Rash, liver function test abnormalities and edema/fluid retention were each reported as SAEs in a low number (<3%) of GIST patients, in common with the experience in the CML population.

### B. Description of Patient Exposure Per Sponsor

Table 13 (Sponsor Table 2-1 of ISS) summarizes the duration of exposure. The listing for imatinib dose is based on the initial dose to which patients were assigned. The percentage of patients on study drug for varying lengths of time were similar in the two dose groups. At data cut-off, the mean period of exposure to study drug for the entire population was approximately seven months.

**Table 13 : Duration of Exposure**

| Initial dose (mg/day) Duration of exposure* | 400 mg (N=73) | 600 mg (N=74) | All doses (N=147) |
|---|---|---|---|
| ≤ 6 months | 26 (35.6) | 24 (32.4) | 50 (34.0) |
| > 6 – ≤ 12 months | 41 (56.2) | 46 (62.2) | 87 (59.2) |
| > 12 – ≤ 18 months | 6 (8.2) | 4 (5.4) | 10 (6.8) |
| Total | 73 100%) | 74 (100%) | 147 (100%) |

* Duration of exposure = last date of study medication minus start date plus 1 (i.e. interruption periods are included in the calculation of duration of exposure). One month is regarded as 4 weeks (Sponsor Table 2-1 of ISS)

Dose interruption and discontinuation due to AEs are summarized in Table 14. A variety of AEs resulted in dose adjustments, the most common being edema, nausea, vomiting, diarrhea, neutropenia and rash. This closely resembles the experience with imatinib in the treatment of CML patients. Because of small numbers no analyses by age, gender or race were performed.

**Table 14 : Dose Interruptions and Dose Discontinuations Due to AEs**

| Initial dose (mg/day)<br>Number of patients | 400 mg (N=73)<br>n (%) | 600 mg (N=74)<br>n (%) | All doses (N=147)<br>n (%) |
|---|---|---|---|
| AEs leading to dose interruptions | 29 (39.7) | 39 (52.7) | 68 (46.3) |
| Drug Permanently D/C | 6 (8) | 6 (8) | 12 (8) |

(Sponsor Table 2-2 of ISS)

Patient disposition at the time of data cut-off for the interim analysis (10 July 2001) is summarized in Table 15 (sponsor table 4-1 of ISS). The study is ongoing and 122 patients (83%) continue study medication. No patient has yet completed two full years of therapy. Twenty-five patients (17%) have discontinued the study, the most frequent reason being 'unsatisfactory therapeutic effect'. One patient randomized to receive 400 mg had no measurable lesions. This patient never received study medication.

**Table 15 : Patient Disposition**

| Initial dose (mg/day) | 400 mg n (%)[1] | 600 mg n (%)[1] | All doses n (%)[1] |
|---|---|---|---|
| Randomized | 74 | 74 | 148 |
| Treated | 73 | 74 | 147 |
| Ongoing | 61 (83.6) | 61 (82.4) | 122 (83.0) |
| Completed Study | 0 | 0 | 0 |
| Withdrawn from Study | 12 (16.4) | 13 (17.6) | 25 (17.0) |
| Reasons for Withdrawal | | | |
| Adverse Event | 2 (2.7) | 3 (4.1) | 5 (3.4) |
| Abnormal Laboratory Values | 0 | 2 (2.7) | 2 (1.4) |
| Unsatisfactory Therapeutic Effect | 5 (6.8) | 6 (8.1) | 11 (7.5) |
| Protocol Violation | 1 (1.4) | 0 | 1 (0.7) |
| Subject Withdrew Consent | 0 | 2 (2.7) | 2 (1.4) |
| Lost to Follow-up | 0 | 0 | 0 |
| Death | 4 (5.5) | 0 | 4 (2.7) |

[1] Percentage based on the TRT population (sponsor table 4-1 of ISS)

## C. Methods and Specific Findings of Safety Review

Safety assessments consisted of monitoring and recording all adverse events (AEs) and SAEs (with their severity and relationship to study drug), the regular monitoring of hematology, and blood chemistry, regular measurement of vital signs, the performance of physical examinations and documentation of all concomitant medications and therapies.

Narratives were provided for the following events:

- Deaths other than from disease progression
- Patients who discontinued for treatment-related SAEs
- All study-drug-related SAEs
- Specific, clinically important SAEs regardless of study drug relationship including: rash, liver enzyme abnormalities, fluid retention and edema, renal toxicity, intra-tumoral hemorrhage, GI tract hemorrhage, and cerebral hemorrhage
- Other clinically significant AEs

AEs were summarized for each dosing cohort by the type of AE and the maximum severity according to National Cancer Institute (NCI) Common Toxicity Criteria (CTC). Laboratory data were analyzed, whenever possible, using the NCI CTC grading system. Abnormal laboratory values or test results constituted an AE only if associated with clinical signs or symptoms or requiring therapy.

Table 16 (Sponsor Table 5-2 of ISS) lists the sponsor's analysis of the number and percentage of patients with AEs that occurred in more than 10% of the patients in B2222, regardless of attribution to treatment.

**Table 16 : Number (%) of Patients with AEs**

| | All CTC Grades | | | CTC Grade 3/4 | | |
|---|---|---|---|---|---|---|
| **Initial dose (mg/day)** | **400 mg (N=73)** | **600 mg (N=74)** | **All doses (N=147)** | **400 mg (N=73)** | **600 mg (N=74)** | **All doses (N=147)** |
| **Preferred Term** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Nausea | 39 (53.4) | 42 (56.8) | 81 (55.1) | 2 (2.7) | 2 (2.7) | 4 (2.7) |
| Diarrhea NOS | 33 (45.2) | 42 (56.8) | 75 (51.0) | 1 (1.4) | 4 (5.4) | 5 (3.4) |
| Periorbital edema | 32 (43.8) | 37 (50.0) | 69 (46.9) | 0 | 0 | 0 |
| Fatigue | 24 (32.9) | 28 (37.8) | 52 (35.4) | 1 (1.4) | 0 | 1 (0.7) |
| Muscle cramps | 22 (30.1) | 30 (40.5) | 52 (35.4) | 0 | 0 | 0 |
| Headache NOS | 18 (24.7) | 26 (35.1) | 44 (29.9) | 0 | 0 | 0 |
| Abdominal pain NOS | 21 (28.8) | 19 (25.7) | 40 (27.2) | 5 (6.8) | 1 (1.4) | 6 (4.1) |
| Dermatitis NOS | 14 (19.2) | 25 (33.8) | 39 (26.5) | 1 (1.4) | 2 (2.7) | 3 (2.0) |
| Vomiting NOS | 16 (21.9) | 17 (23.0) | 33 (22.4) | 1 (1.4) | 2 (2.7) | 3 (2.0) |
| Flatulence | 12 (16.4) | 17 (23.0) | 29 (19.7) | 0 | 0 | 0 |
| Edema lower limb | 19 (26.0) | 9 (12.2) | 28 (19.0) | 0 | 0 | 0 |
| Nasopharyngitis | 9 (12.3) | 10 (13.5) | 19 (12.9) | 0 | 0 | 0 |
| Anemia NOS | 7 (9.6) | 10 (13.5) | 17 (11.6) | 3 (4.1) | 3 (4.1) | 6 (4.1) |
| Insomnia NEC | 8 (11.0) | 8 (10.8) | 16 (10.9) | 0 | 0 | 0 |
| Edema NOS | 5 (6.8) | 10 (13.5) | 15 (10.2) | 2 (2.7) | 0 | 2 (1.4) |
| Back pain | 8 (11.0) | 7 (9.5) | 15 (10.2) | 1 (1.4) | 0 | 1(0.7) |
| Face edema | 6 (8.2) | 9 (12.2) | 15 (10.2) | 1 (1.4) | 0 | 1(0.7) |
| Pyrexia | 9 (12.3) | 4 (5.4) | 13 (8.8) | 0 | 0 | 0 |
| Lacrimation increased | 4 (5.5) | 8 (10.8) | 12 (8.2) | 0 | 0 | 0 |
| Upper respiratory tract infection NOS | 4 (5.5) | 8 (10.8) | 12 (8.2) | 0 | 0 | 0 |
| Taste disturbance | 1 (1.4) | 10 (13.5) | 11 (7.5) | 0 | 0 | 0 |

(Sponsor Table 5-2 of ISS)

Events relating to the GI system with nausea and diarrhea occurred most frequently (in 55.1% and 51.0% of patients, respectively). GI tract-related AEs together accounted for the greatest number of patients with grade 3/4 events in the study population, including six patients (five at the 400 mg dose) with abdominal pain, and five (four at 600 mg) with diarrhea.

Edema was the next most frequently reported AE and was characterized as either periorbital (47% of patients), lower limb (19% of patients) or facial (10% of patients). In 10% of patients, edema was reported without the site of edema being specified. For two patients in the 400 mg dose group, the severity was grade 3 (one patient had both grade 3 edema NOS and grade 3 facial edema).

For some AEs (diarrhea, periorbital edema, muscle cramps, headache and dermatitis), there was a higher number of patients in the 600 mg dose group. However, over twice as many patients in the 400 mg dose group had lower extremity edema (26% vs 12.2%, respectively).

To simplify the presentation, grouping of preferred terms for some commonly occurring AEs was performed. This grouping is identical to the grouping used in the registration studies with imatinib in CML patients except that tumor hemorrhage was introduced as an additional group for the GIST patient population.

Table 17 (Sponsor Table 5-3 of ISS) lists the sponsor's analysis of the number of patients with grouped AEs .

**Table 17 : Number of Patients with Grouped AEs**

| | All CTC grades | | | CTC Grade 3 / 4 | | |
|---|---|---|---|---|---|---|
| **Initial dose (mg/day)** | **400 mg (N=73)** | **600 mg (N=74)** | **All doses (N=147)** | **400 mg (N=73)** | **600 mg (N=74)** | **All doses (N=147)** |
| **Grouped AEs** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Fluid retention | 51 (69.9) | 56 (75.7) | 107 (72.8) | 4 (5.5) | 2 (2.7) | 6 (4.1) |
| Superficial edema | 51 (69.9) | 55 (74.3) | 106 (72.1) | 3 (4.1) | 0 | 3 (2.0) |
| Other fluid retention | 5 (6.8) | 4 (5.4) | 9 (6.1) | 1 (1.4) | 2 (2.7) | 3 (2.0) |
| Muscle cramps | 22 (30.1) | 30 (40.5) | 52 (35.4) | 0 | 0 | 0 |
| Myalgia | 5 (6.8) | 1 (1.4) | 6 (4.1) | 0 | 0 | 0 |
| Musculoskeletal pain | 14 (19.2) | 8 (10.8) | 22 (15.0) | 2 (2.7) | 0 | 2 (1.4) |
| Joint pain | 1 (1.4) | 6 (8.1) | 7 (4.8) | 0 | 0 | 0 |
| Any hemorrhage | 12 (16.4) | 13 (17.6) | 25 (17.0) | 3 (4.1) | 6 (8.1) | 9 (6.1) |
| Tumor hemorrhage | 1 (1.4) | 3 (4.1) | 4 (2.7) | 1 (1.4) | 3 (4.1) | 4 (2.7) |
| Cerebral hemorrhage | 1 (1.4) | 0 | 1 (0.7) | 1 (1.4) | 0 | 1 (0.7) |
| GI tract hemorrhage | 4 (5.5) | 4 (5.4) | 8 (5.4) | 3 (4.1) | 1 (1.4) | 4 (2.7) |
| Abdominal pain | 27 (37.0) | 27 (36.5) | 54 (36.7) | 5 (6.8) | 2 (2.7) | 7 (4.8) |
| Rash | 19 (26.0) | 28 (37.8) | 47 (32.0) | 2 (2.7) | 2 (2.7) | 4 (2.7) |

(Sponsor Table 5-3 of ISS)

*Reviewer comment : During discussion of labeling of AE's for GIST, the sponsor revised the total percentage of 'Any hemorrhage/All grades' to 400 mg All grades = 18% and 600 mg All grades = 19% because they detected one additional patient that had events that fell into this category in each dose level (patient 502/098 CVA at 400 mg ; patient 502/073 duodenal ulcer at 600 mg).*

Common Toxicity Criteria 3 and 4 biochemical abnormalities are listed in Table 18 (Sponsor Table 6-1 of ISS) and hematologic abnormalities are listed in Table 19 (Sponsor Table 6-2 of ISS). These data were presented in the application as " grade ½ values at baseline that then increased in severity to grade ¾ ". The grade ½ category at baseline in Tables 18 and 19 below does not report all patients who experienced a grade ½ AE in each category.

**Table 18 : Biochemical Abnormalities**

| Laboratory Parameter<br>CTC grading | 400 mg<br>(N=73)<br>n (%) | 600 mg<br>(N=74)<br>n (%) | All doses<br>(N=147)<br>n (%) |
|---|---|---|---|
| Creatinine | | | |
| grade 1/2 at baseline | 3 (4.1) | 5 (6.8) | 8 (5.4) |
| grade 3 | 0 | 2 (2.7) | 2 (1.4) |
| grade 4 | 1 (1.4) | 0 | 1 (0.7) |
| Albumin | | | |
| grade 1/2 at baseline | 32 (43.8) | 29 (39.2) | 61 (41.5) |
| grade 3 | 2 (2.7) | 3 (4.1) | 5 (3.4) |
| grade 4 | 0 | 0 | 0 |
| Bilirubin | | | |
| grade 1/2 at baseline | 4 (5.5) | 1 (1.4) | 5 (3.4) |
| grade 3 | 1 (1.4) | 1 (1.4) | 2 (1.4) |
| grade 4 | 0 | 2 (2.7) | 2 (1.4) |
| Alkaline Phosphatase | | | |
| grade 1/2 at baseline | 32 (43.8) | 26 (35.1) | 58 (39.5) |
| grade 3 | 0 | 1 (1.4) | 1 (0.7) |
| grade 4 | 0 | 0 | 0 |
| SGOT (AST) | | | |
| grade 1/2 at baseline | 16 (21.9) | 16 (21.6) | 32 (21.8) |
| grade 3 | 2 (2.7) | 1 (1.4) | 3 (2.0) |
| grade 4 | 0 | 1 (1.4) | 1 (0.7) |
| SGPT (ALT) | | | |
| grade 1/2 at baseline | 11 (15.1) | 8 (10.8) | 19 (12.9) |
| grade 3 | 2 (2.7) | 3 (4.1) | 5 (3.4) |
| grade 4 | 0 | 0 | 0 |

**Table 19 : Hematological Abnormalities**

| Laboratory Parameter CTC grading | 400 mg (N=73) n (%) | 600 mg (N=74) n (%) | All doses (N=147) n (%) |
|---|---|---|---|
| Hemoglobin | | | |
| grade 1/2 at baseline | 37 (50.7) | 33 (44.6) | 70 (47.6) |
| grade 3 | 2 (2.7) | 3 (4.1) | 5 (3.4) |
| grade 4 | 0 | 1 (1.4) | 1 (0.7) |
| Leukocytes | | | |
| grade 1/2 at baseline | 3 (4.1) | 12 (16.2) | 15 (10.2) |
| grade 3 | 1 (1.4) | 5 (6.8) | 6 (4.1) |
| grade 4 | 0 | 0 | 0 |
| Platelets | | | |
| grade 1/2 at baseline | 1 (1.4) | 6 (8.1) | 7 (4.8) |
| grade 3 | 0 | 1 (1.4) | 1 (0.7) |
| grade 4 | 0 | 0 | 0 |
| Neutrophils | | | |
| grade 1/2 at baseline | 2 (2.7) | 8 (10.8) | 10 (6.8) |
| grade 3 | 2 (2.7) | 4 (5.4) | 6 (4.1) |
| grade 4 | 2 (2.7) | 3 (4.1) | 5 (3.4) |
| Lymphocytes | | | |
| grade 1/2 at baseline | 30 (41.1) | 37 (50.0) | 67 (45.6) |
| grade 3 | 4 (5.5) | 11 (14.9) | 15 (10.2) |
| grade 4 | 0 | 0 | 0 |

(Sponsor Table 6-2 of ISS)

Deaths

Ten patients have died, 7 (9.6%) on the 400 mg arm and 3 (4.1%) on the 600 mg arm at the time of cutoff for the interim analysis. The time to death since the start of treatment ranged from 12 to 35.7 weeks in the 400 mg group and from 5.3 to 32.7 weeks in the 600 mg group. Six deaths were attributed to PD, three in each dose group. Four additional patients (all in the 400-mg cohort) died as a result of AEs which were not suspected to be related to study drug. The causes were listed as pulmonary embolism, respiratory failure, cerebrovascular accident and cardiac arrest, respectively.

Sponsor's Summary

The overall safety profile of imatinib was similar in the GIST patients treated in B2222 to the much larger number of patients treated with CML and other Philadelphia chromosome-positive leukemias. An exception was in the occurrence of hemorrhagic events.

All patients (100%) in B2222 experienced at least one AE, though the majority (90%) was of CTC grade 1/2 severity. Grade 3/4 AEs were reported in 37% of patients. A suspected relationship to the study drug was attributed by the investigator in 66% of AE's.

With respect to individual AE's, most patients had events relating to the GI system with nausea and diarrhea occurring most frequently (in 55.1% and 51.0% of patients, respectively). Other GI events, including abdominal pain, vomiting and flatulence, were less commonly reported. Individual edema AE's were the next most frequently reported AE, characterized as periorbital (47% of patients), lower limb (19% of patients) and facial (10% of patients). Other AE's noted in >25% of patients were fatigue, muscle cramps, headache and dermatitis.

The effect of imatinib dose on the occurrence of AE's is uncertain because of the low numbers of patients in each dose group. For some of the AE's (diarrhea, edema, muscle cramps, headache and dermatitis) there was an increase in the number of patients in the 600 mg dose group whereas for another (lower extremity edema), over twice as many patients in the 400 mg dose group as compared to the 600 mg dose group had this AE.

Four patients discontinued due to AE's with a suspected relationship to study drug. One patient in the 400 mg dose group discontinued treatment for GI bleeding, and three patients in the 600 mg dose group discontinued treatment for exacerbation of pulmonary disease, elevated transaminases, and agitation and fatigue, respectively.

SAE's were reported in 29% of patients but had a suspected relationship to study drug in only 12% of patients. SAE's associated with the GI system were reported most frequently (in 11% of patients). As in CML patients, rash, liver function test abnormalities and episodes of edema and/or fluid retention were each reported as SAE's in a small number of patients.

Seven patients in study B2222 experienced GI or intra-tumoral hemorrhage. Some of the GI hemorrhages may have been due to the rupture of tumor masses within the wall of the stomach or intestine. The occurrence of bleeding did not correlate with low platelet counts, large tumor burden or the duration of therapy with imatinib. GI and intra-tumoral hemorrhages were also reported in eight GIST patients in other on-going studies with imatinib, three of which had a fatal outcome.

Ten patients died during study B2222 (by the time of data cutoff for the interim analysis) and an additional two patients died within 28 days of discontinuing study drug. None of these deaths was suspected to be related to the trial medication.

## FDA Analysis

The FDA analysis of AE's was conducted, using raw and derived AE, LABH and LABB datasets provided electronically by the sponsor. Narratives that were provided were also reviewed. The format for this review will be to comment on each of the sponsor's safety tables.

Exposure to imatinib was calculated by the sponsor using the cutoff date for this report (July 10, 2001). Since patients were likely not to have been seen on this date to confirm they were still taking study medication, a more conservative way of calculating drug exposure was to use the date of last patient assessment. Table 20 provides this data. The maximum imatinib exposure for 400 mg/d and 600 mg/d was 288 and 291 days, respectively.

**Table 20 : Duration of Exposure**

| Initial dose (mg/day) | 400 | 600 | All doses |
|---|---|---|---|
| Duration of exposure* | (N=73) | (N=74) | (N=147) |
| ≤ 6 months | 58 (79) | 54 (73) | 112 (76) |
| > 6 – ≤ 12 months | 15 (21) | 20 (27) | 35 (24) |
| Total | 73 (100) | 74 (100) | 147 (100) |

- One month is regarded as 4 weeks

Dose interruptions and dose discontinuations due to AE's and patient disposition were comparable in the sponsor and FDA analyses. See Tables 14 and 15.

Minor discrepancies were observed in comparing sponsor and FDA analyses of the adverse events listed in Table 16. In contrast to the sponsor's analysis, edema was the most frequent side effect noted in the FDA analysis because edema events were grouped. External (superficial) and/or internal edema occurred in 107 patients, while nausea occurred in 80 patients. FDA-sponsor differences in numbers of patients with grade 3/4 AE's were less frequent than were differences in numbers of grade 1/2 AE's. In total, three more patients had grade 3/4 AE's in the FDA analysis than in the sponsor analysis : 1 periorbital edema (400 mg dose), 1 abdominal pain NOS (600 mg dose), and 1 dermatitis NOS (600 mg dose). As regards grade 1/2 AE's, 1 less patient had nausea (400 mg dose), 1 additional patient had diarrhea (400 mg dose), 9 additional patients had periorbital edema (4-400 mg dose, 5-600 mg dose), 1 less patient had fatigue (600 mg dose), 3 additional patients had muscle cramps (400 mg dose), 1 additional patient had dermatitis NOS (600 mg dose), 1 additional patient had vomiting (600 mg dose), 8 additional patients had extremity edema (1-400 mg dose, 7-600 mg dose), 3 fewer patients had abdominal pain NOS (400 mg dose), and 1 less patient had upper respiratory tract infection NOS (400 mg dose). The frequency of occurrence of nasopharyngitis could not be confirmed as it is unclear what terms the sponsor used to define this toxicity. Possible terms for nasopharyngitis might have included nasal congestion, sinus congestion, postnasal drip, throat constriction and throat tightness.

The likely reason for differences in sponsor and FDA totals for adverse events is the terms used to classify the adverse event. For example, diarrhea could be classified as only diarrhea or as a combination of diarrhea and loose stools. Muscle cramps were classified as *cramps* or *mylagia* or *muscle* in the FDA analysis. Abdominal pain might include abdominal pain alone, abdominal pain combined with abdominal cramps, and/or with abdominal discomfort. It was classified as abdominal pain and abdominal cramps in the FDA analysis. In the edema category, extremity edema might, or might not, include ankle, foot, hand, and arm edema. All terms were used in the FDA analysis. Periorbital edema might, or might not, also include eyelid edema. Both terms were used in the FDA analysis.

In both the sponsor and FDA analysis there was a low frequency of grade ¾ edema, both external (superficial) and internal. Imatinib 600 mg/day was not associated with an increased frequency or severity of edema compared to the 400 mg/day dose.

Because the biggest difference between FDA and sponsor analysis was in the category of edema, Table 21 summarizes FDA results. There were 107 distinct patients with external edema and 5 patients who had either ascites or pleural effusion. In the external edema category, patients may have had more than one edema site.

**Table 21 : Number of Patients with Edema**

| | All CTC grades | | | CTC Grade 3 / 4 | | |
|---|---|---|---|---|---|---|
| **Initial dose (mg/day)** | **400 mg (N=73)** | **600 mg (N=74)** | **All doses (N=147)** | **400 mg (N=73)** | **600 mg (N=74)** | **All doses (N=147)** |
| **AE** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| External edema (Total) | 52 (71.2) | 55 (74.3) | 107 (72.8) | 3 (4.1) | 0 | 3 (2.0) |
| Periorbital | 36 (49.3) | 42 (56.8) | 78 (53.1) | 0 | 0 | 0 |
| Face edema | 38 (52.1) | 49 (66.2) | 87 (59.2) | 1 (1.4) | 0 | 1 (0.7) |
| Extremity edema | 20 (27.4) | 16 (21.6) | 36 (24.5) | 1 (1.4) | 0 | 1 (0.7) |
| NOS | 3 (4.1) | 10 (13.5) | 13 (8.8) | 1 (1.4) | 0 | 1 (0.7) |
| Internal edema | | | | | | |
| Ascites | 2 (2.7) | 1 (1.4) | 3 (2.0) | 1 (1.4) | 1 (1.4) | 2 (1.4) |
| Pleural Effusion | 2 (2.7) | 2 (2.7) | 4 (2.6) | 0 | 1 (1.4) | 1 (0.7) |

Hemorrhage within or outside of the gastrointestinal tract, was an AE seen in GIST patients but not in CML patients. This AE is summarized in Table 22. In 7 patients who had eight events of grade ¾ hemorrhage into the tumor or GI tract, there was no apparent correlation between tumor load or response. Onset of tumor hemorrhage was from 6 days to 256 days from the start of therapy (median 137 days). Gastrointestinal bleeding onset was from 6 days to 88 days from the start of therapy (median 29 days).

**Table 22 : Number of Patients with Hemorrhage**

| | All CTC grades | | | CTC Grade 3 / 4 | | |
|---|---|---|---|---|---|---|
| **Initial dose (mg/day)** | **400 mg (N=73)** | **600 mg (N=74)** | **All doses (N=147)** | **400 mg (N=73)** | **600 mg (N=74)** | **All doses (N=147)** |
| **Hemorrhage site** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Tumor | 1 (1.4) | 3 (4.1) | 4 (2.7) | 1 (1.4) | 3 (4.1) | 4 (2.7) |
| Gastrointestinal tract | 4 (5.5) | 4 (5.4) | 8 (5.4) | 3 (4.1) | 1 (1.4) | 4 (2.7) |
| Cerebral | 1 (1.4) | 0 | 1 (0.7) | 1 (1.4) | 0 | 1 (0.7) |
| Other (respiratory, skin, eye) | 7 (9.6) | 5 (6.8) | 12 (8.2) | 0 | 0 | 0 |
| Any | 13 (17.7) | 12 (16.3) | 25 (17.0) | 5 (6.8) | 4 (5.4) | 9 (6.1) |

Hepatic and renal toxicity and hematologic toxicity are summarized in Tables 23 and 24, respectively. The 4 patients with grade 3/4 bilirubin elevation all had hepatic metastases as did the 4 patients with grade 3/4 SGOT elevation. All 5 patients with grade 3/4 SGPT elevation similarly had hepatic metastases. It was not possible to determine how many patients had elevation of serum creatinine secondary to ureteral obstruction by pelvic tumor but several patients were noted to have unilateral or bilateral hydronephrosis on pelvic CT evaluation.

**Table 23 : Hepatic and Renal Biochemical Abnormalities**

| | All CTC grades | | | CTC Grade 3 / 4 | | |
|---|---|---|---|---|---|---|
| **Initial dose (mg/day)** | **400 mg (N=73)** | **600 mg (N=74)** | **All doses (N=147)** | **400 mg (N=73)** | **600 mg (N=74)** | **All doses (N=147)** |
| **Test** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Bilirubin | 17 (23.3 | 16 (21.6) | 33 (22.4) | 1 (1.4) | 3 (4.1) | 4 (2.7) |
| SGOT | 33 (45.2) | 40 (54.1) | 73 (49.7) | 2 (2.7) | 2 (2.7) | 4 (2.7) |
| SGPT | 25 (34.2) | 25 (33.8) | 50 (34.0) | 2 (2.7) | 3 (4.1) | 5 (3.4) |
| Creatinine | 16 (21.9) | 18 (24.3) | 34 (23.1) | 1 (1.4) | 2 (2.7) | 3 (2.1) |

CTC grade 3 / 4 liver function abnormalities were somewhat more frequent in GIST patients than in chronic phase CML patients receiving imatinib 400 mg/day. In the latter population grade 3 / 4 bilirubin, SGOT and SGPT elevations occurred in 0.4%, 1.1% and 1.7%, respectively.

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**Table 24 : Hematologic Abnormalities**

| | All CTC grades | | | CTC Grade 3 / 4 | | |
|---|---|---|---|---|---|---|
| **Initial dose (mg/day)** | **400 mg (N=73)** | **600 mg (N=74)** | **All doses (N=147)** | **400 mg (N=73)** | **600 mg (N=74)** | **All doses (N=147)** |
| **Test** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Hemoglobin | 68 (93.2) | 71 (95.9) | 139 (94.6) | 3 (4.1) | 4 (5.4) | 7 (4.8) |
| White Blood Cells | 41 (56.2) | 55 (74.3) | 96 (65.3) | 1 (1.4) | 5 (6.8) | 6 (4.1) |
| Neutrophils | 29 (39.7) | 34 (45.9) | 63 (42.9) | 4 (5.4) | 7 (9.5) | 11 (7.5) |
| Platelets | 13 (17.8) | 21 (28.4) | 34 (23.1) | 0 | 1 (1.4) | 1 (0.7) |

More patients in the 600 mg cohort had grade 1/2 abnormalities of white blood cell, platelet, neutrophil and lymphocyte counts at baseline, though comparatively few patients developed grade 3/4 values during the course of the trial. As expected hematologic toxicity in GIST patients was less severe than in CML patients. In chronic phase CML patients receiving imatinib 400 mg/day, 5 % had grade 3/4 anemia, 33% grade 3/4 neutropenia and 17% grade 3/4 thrombocytopenia.

## D. Adequacy of Safety Testing

The FDA has reviewed safety data from over 1,300 patients receiving Gleevec™ either for chronic myelogenous leukemia or GIST. Overall, treatment has been well tolerated and dose adjustments and/or temporary dose interruptions have allowed patients to be maintained on study. In the GIST study only 12 of 147 patients had treatment permanently discontinued prior to progression, with non-AE factors accounting for discontinuation in 5 of those patients (death 3, unsatisfactory therapeutic effect 1, withdrawal of consent 1).

Unfortunately, long duration imatinib safety data is not available, as yet. At the time of the 120 day CML safety update there were relatively few CML patients who had received more than 1 year of treatment. Most of the GIST patient population has also received less than one year of treatment. Longer follow-up will be required to determine imatinib chronic adverse effects.

## E. Summary of Critical Safety Findings and Limitations of Data

Review of safety data for Gleevec™ in the treatment of advanced, metastatic GIST tumors revealed no surprises from data already reviewed for Gleevec™ treatment of

CML. Imatinib was relatively well tolerated in the GIST patient population. The study drug was only rarely permanently discontinued because of an AE. The only toxicity more frequently seen in GIST patients than in CML is hemorrhage and slightly more frequent grade ¾ elevations in bilirubin, SGOT, and SGPT. The presumed pathogenesis of hemorrhage in GIST is invasion of a blood vessel wall by tumor followed by rupture of the wall after tumor cell death. The GIST patients with grade ¾ elevations of bilirubin, SGOT and SGPT had liver metastases. There was no striking difference in AE's in the Gleevec™ 600 mg/day group compared to the 400 mg/day group.

The major limitation of present data is the relatively small number of GIST patients enrolled in the present study. Additional information will soon be available, from larger trials being conducted.

## VIII. Dosing, Regimen, and Administration Issues

In patients with CML, the recommended dosage is 400 mg/day for patients in chronic phase and 600 mg/day for patients in accelerated phase or blast crisis.

A dose of 400 mg daily or 600 mg daily will be recommended in GIST patients. In the GIST clinical trial, patients were randomized to a dose of 400 mg/day or 600 mg/day. However, the study was not powered to detect a statistically significant difference in objective response rates between the two dosing regimens and no such difference was observed. Small differences in the safety profile between the two dose levels studied did not permit a conclusion that the risk/benefit ratio of one dose level was superior to the other.

The GIST study allowed patients with progressive disease on a dose of 400 mg daily to have a dose increase to 600 mg daily. Of 12 patients who were randomized to 400 mg daily and had dose increases to 600 mg daily for progressive disease, none had a subsequent confirmed assessment of a complete or partial response. The relevance of stable disease reported in two patients is unclear, particularly with the limited followup in the study.

The EORTC phase 1 study of imatinib in patients with GIST and soft tissue sarcomas consisted of dose escalations up to a dose of 500 mg BID (1000 mg/day). At this dose level, 3 patients had grade 3 nausea/vomiting, 1 had grade 3 edema, and one had grade 3 dyspnea. Dosing at 400 mg BID (800 mg/day) was well tolerated with dose limiting neutropenia noted in only one patient. Further information regarding efficacy and safety of dosing at 800 mg/day in GIST patients will be available from the ongoing NCI and EORTC sponsored trials of 400 mg/day vs 800 mg/day of imatinib.

# IX. Use in Special Populations

## A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Eighty-three males and sixty-four females were enrolled and randomized on the GIST trial. No obvious differences in the safety or efficacy profiles were noted between males and females. No obvious differences in the pharmacokinetic profile of the drug were noted between males and females.

## E. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

1. Age

In the GIST study, 29% of patients were older than 60 years and 10% were older than 70 years. No obvious differences in the safety or efficacy profiles were noted in patients older than 65 years as compared to younger patients, but the small patient numbers makes drawing definitive conclusions impossible.

2. Race/Ethnicity

The majority of patients in the GIST trial were Caucasian (92.5%). No ethnic/racial specific analyses were conducted due to the small patient numbers.

### C. Evaluation of Pediatric Program

A phase 1 study of imatinib in children with Ph+ leukemias is ongoing. GIST tumors are not considered relevant to the pediatric population, as these tumors occur in adults.

### D. Comments on Data Available or Needed in Other Populations

1. Renal or Hepatic Impairment

No studies in renal or hepatic impaired patients have been completed. There is an ongoing PK study in CML patients with liver impairment.

2. Pregnancy

Imatinib should not be used in pregnant females. It is currently classified as pregnancy class D due to its teratogenic effects in rats and rat fetal loss after post-implantation exposure. No reports of exposure during pregnancy have been received in the post-marketing database. The sponsor is encouraged to submit any data regarding inadvertent use in pregnant women from the post-marketing experience.

## X. Conclusions and Recommendations

### A. Conclusions

The FDA reviewers' view of the benefits and risks of imatinib for the recommended indication are outlined below.

The assessment of benefit is based on the surrogate endpoint of objective response. The efficacy result for this surrogate endpoint can be summarized as an overall objective partial response rate of 38% (56/147) and partial response rates of 33% (24/73) and 43% (32/74) for the 400 mg and 600 mg dose groups respectively. For metastatic or unresectable malignant GIST, the effect of imatinib treatment measured by this surrogate endpoint is better than would be expected with available therapy, since for patients with unresectable disease, no effective therapy exists, and for patients with metastatic disease, chemotherapy is associated with essentially no response and surgery at best offers a temporary palliative benefit.

With regard to risks associated with Gleevec™ therapy, the FDA review of Gleevec™ in patients with chronic myelogenous leukemia had previously identified a number of safety concerns, and review of the database of patients with recurrent or metastatic GIST has allowed identification of the following toxicities :

Nausea: As in patients with CML, nausea is encountered in more than half of all patients with GIST receiving imatinib.

Edema and fluid retention : As in patients with CML, most patients with GIST receiving imatinib have superficial edema and some patients have more serious but rarely life-threatening fluid retention.

Cytopenias : Imatinib was noted in the prior review to decrease the number of white blood cells and platelets in patients with CML, increasing the risk of infection and risk of bleeding. In patients with GIST, lowering of white blood cells and platelets occurs less commonly, possibly due to the lack of any underlying bone marrow pathology in most patients.

Hemorrhage : Bleeding was observed in nearly 20% of GIST patients receiving imatinib. In seven patients, imatinib was associated with bleeding into the tumor or gastrointestinal tract. One patient with a cerebrovascular accident was reported.

Liver toxicity : Elevations in liver transaminases have been noted in patients with CML as well as patients with GIST. Monitoring is especially important in patients with GIST, since many of these patients also have metastatic disease in the liver.

Drug-drug interactions : Significant drug-drug interactions have been previously observed with imatinib. Imatinib is metabolized by, and also inhibits, hepatic P450 isoenzyme CYP3A4. There is also the potential for significant interactions with drugs metabolized by CYP2D6 and CYP2C9 as these enzymes have been demonstrated in in vitro studies to play a minor role in imatinib metabolism.

Potential immunosuppression : Imatinib causes lymphopenia .

In the GIST clinical trial, patients were randomized to a dose of 400 mg/day or 600 mg/day. However, the study was not powered to detect a statistically significant difference in objective response rates between the two dosing regimens and no such difference was observed. Small differences in the safety profile between the two dose levels studied did not permit a conclusion that the risk/benefit ratio of one dose level was superior to the other.

It is the clinical judgement of the FDA clinical review team that the potential benefits outweigh the risks associated with imatinib treatment of advanced GIST using a dose of 400 mg or 600 mg daily. However, it should be emphasized that the duration of followup in patients with GIST treated with imatinib is limited at this point. Therefore, new safety data from ongoing trials should be evaluated promptly by Novartis and new information communicated to physicians and patients.

## B. Recommendations

1. Approval

The Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA recommends approval of Gleevec™ (imatinib mesylate capsule) for the treatment of patients with metastatic or unresectable malignant gastrointestinal stromal tumors (GIST). The recommended dose is 400 mg or 600 mg daily as there was no signifcant difference in the risk/benefit ratio between the two dose levels evaluated in trial B2222.

We recommend approval under subpart H (accelerated approval) of the NDA regulations. Accelerated approval under subpart H applies to drugs for serious or life-threatening diseases. For indications where the new drug appears to provide benefit over available therapy, FDA may grant accelerated approval based on a surrogate endpoint that is reasonably likely to predict clinical benefit. After approval, the sponsor is required to perform a post-marketing study to demonstrate that treatment is associated with clinical benefit. If the studies fail to demonstrate clinical benefit or if the sponsor does not show due diligence, the drug may be removed from the market.

2. Binding phase 4 commitments

The following should be completed by the sponsor for conversion to a full approval

A. Complete the follow-up on sNDA trial B2222 and submit mature response rate, response duration, and survival data. The suggested timlines for these submissions are December 31, 2002 for response and response duration, and after either 70% of events have occurred or at the 5 year follow-up for survival analysis (March 31, 2007).

B. An updated report of the central pathology review for sNDA trial B2222 should be submitted when review of the 13 pending cases is complete (June 2002).

C. Submit data from the two ongoing multicenter trials of imatinib testing 400 mg/day versus 800 mg/day in patients with GIST (EORTC and NCI sponsored trials). Response rate, duration of response, safety and survival data should be submitted. The data should be submitted in a timeline consistent with the statistical analysis plan of each respective protocol (estimated June 2003).

D. Submit clinical and PK data for the EORTC phase 1 study of imatinib in patients with GIST and other soft-tissue sarcomas (Submission July 31, 2002).

E. Assure availability of a validated test kit for detection of CD117 tumor expression by immunohistochemistry. Timelines are as follows :
Pre-Market Application (PMA) filing by 3rd party planned by December 31, 2002

*See executive summary for other phase 4 commitments*



# XI. Appendix

## A. SWOG Response Criteria

### DISEASE STATUS

**Measurable Disease**

Bidimensionally measurable lesions with clearly defined margins by 1) medical photograph (skin or oral lesions) or plain X-ray, with at least one diameter 0.5 cm or greater (bone lesions not included) or 2) CT, MRI or other imaging scan, with both diameters greater than the distance between cuts of the imaging study or 3) palpation, with both diameters 2 cm or greater.

**Evaluable Disease**

Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with both diameters less than 0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter less than 2 cm, bone disease.

**Nonevaluable Disease**

Pleural effusions, ascites, disease documented by indirect evidence only (eg, by lab only)

**OBJECTIVE STATUS**

Where there are more than 5 measurable lesions in any one organ system, the five largest lesions should be selected at baseline to be measured throughout the study. The remaining measurable lesions in that organ system will be considered evaluable for the purpose of objective status determination.

**Complete Response (CR)**

Complete disappearance of all measurable and evaluable disease. No new lesions. No disease related symptoms. No evidence of nonevaluable disease, including normalization of markers and other relevant abnormal lab values. *All measurable, evaluable and nonevaluable lesions and sites must be assessed using the same technique as baseline.*

**Partial Response (PR)**

Greater than or equal to 50% decrease from baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. *All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline.*

**Stable Disease/No Response (SD)**

Does not qualify for CR, PR, progression or unknown. *All measurable and evaluable sites must be assessed using the same technique used at baseline.*

**Disease Progression**

50% increase or an increase of 10 $cm^2$ (whichever is smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening from previous assessment of any evaluable disease, OR reappearance of any lesion which had disappeared, OR appearance of any new lesion/site, OR failure to return to evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer). For 'scan-only' bone disease, increased uptake does not constitute clear worsening. Worsening of existing nonevaluable disease does not constitute progression.
Exceptions : (1) In cases for which initial tumor flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms must persist beyond 4 weeks or there must be additional evidence of progression.

(2) Lesions which appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

**Unknown**

Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

**Notes**

1) Nonevaluable disease does not affect objective status except in determination Of CR (all disease must be absent; a patient who otherwise has a CR, but who has nonevaluable disease present or not assessed, will be classified as having a PR) and in determination of progression (if NEW sites of nonevaluable disease develop).

2) The only objective statuses for evaluable disease which apply are CR, stable/no response, progression, and unknown.
3) Objective statuses must stay the same or improve over time until progression (unknown excepted).

**BEST RESPONSE**

Best response is determined from the sequence of objective statuses. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluation (second AFTER the prestudy evaluation) will have a best response of increasing disease. Best response is unknown if the patient does not qualify for a best response of increasing disease and if all objective statuses after the first determination and before progression are unknown.

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