- A documented > grade 3 non-hematologic toxicity that recurs despite dose reduction or is life-threatening such that retreatment with STI 571 would be deemed medically inappropriate is considered Intolerance of Treatment. Treatment with STI 571 should be discontinued and the patient crossed over to the IFN-a + Cytarabine arm.
- If such toxicity occurs after crossover to GLEEVEC, the patient should be discontinued from the study.
-

3.6.3.3 Hematological Toxicity

- If a patient experiences a Grade 3/4 hematological toxicity, STI 571 must be withheld until the toxicity has resolved to < Grade 2. ANC will take precedence over WHC count in determining the degree of neutropenia
- If the toxicity resolves within two weeks, STI 571 may be resumed at a dose of 400 mg daily
- If the Grade 3-4 toxicity recurs or persists for longer than two weeks, STI 571 must be withheld and reduced to 300 mg daily once toxicity has resolved to < Grade 2.
- No dose reductions will be performed for grade 3/4 anemia. Patients developing anemia may be transfused at the discretion of the investigator.

3.6.4 Definition of intolerance to treatment

A documented > grade 3 non-hematologic toxicity that recurs despite dose reduction to a daily dose of 300 mg or is life-threatening such that retreatment with STI 571 would he deemed medically inappropriate. Under these conditions, treatment with STI 571 should be discontinued and the patient crossed over to the IFN-a + Cytarabine arm. If such toxicity occurs after crossover to STI 571, the patient should be discontinued from the study.

3.7. Active control arm: IFN-α combined with Cytarabine

3.7.1 Dose and schedule

- Supplies of IFN-α and Cytarabine were commercially available and will not be supplied by the sponsor. Only recombinant IFN-α should be used. Each center should ensure that IFN-α supplies used during the course of the trial are approved for the treatment of CML in chronic phase in the respective country.

Recombinant IFN-α was administered subcutaneously as induction regimen. The dose of IFN-α could be gradually increased over four weeks of administration to the target dose of 5 MU/m2/day on the following suggested dose escalation scale:

- IFN 3 MU 3 x week for 1 week
- IFN 5 MU 3 x week for 1 week
- IFN 5MU/day for 2 weeks
- IFN 5MU/m^2/day.

- Once the maximum tolerated dose of IFN-α is achieved, Cytarabine will he added at a dose of 20 mg/m2/day (maximum daily dose of 40 mg) for 10 days every month, administered once a day subcutaneously.
- Cytarabine will be discontinued when a complete cytogenetic response is achieved and confirmed by cytogenetic analysis on two consecutive occasions not more than 3 months apart.
- IFN-α therapy will continue to be administered until crossover, progression to accelerated phase, blast crisis or death, or the development of intolerance of treatment, whichever occurs first.

3.7.2 Dose escalation of Cytarabine

The Cytarabine dose may be increased up to 40 mg/day for 15 days each month if a complete hematological response at 3 months or at least a minor cytogenetic response at 12 months is not achieved. Dose escalation of Cytarabine should be considered only when all attempts have been made to administer IFN-α at the maximum tolerated dose, i.e. 5 MU/m2/day.

3.7.3 Dose Reductions

3.7.3.1 Toxicity thought to be IFN-α associated, (fatigue, depression, myalgias)

- Grade 2 toxicity: proceed to a 25% dose reduction of IFN-α
- Grade 3/4 toxicity: interrupt IFN-α until recovery and resume at 50% of the IFN-α dose

3.7.3.2 Thought to be Cytarabine related toxicities (diarrhea and mucositis persisting after appropriate medical management)

- Cytarabine treatment should be discontinued for > grade 3 toxicity.
- Cytarabine may he re-introduced after recovery, at the investigator's discretion.

3.7.3.3 Hematological toxicity > grade 3

- Cytarabine must be interrupted.
- Cytarabine treatment may be resumed if at the time of the next cycle the ANC count $\geq 1.5 \times 10^9$/L and platelet count > 100×10^9/L.
- If patient is on IFN alone, IFN must be held until toxicity ≤ grade 2

3.7.4 Intolerance to treatment

Documented > grade 3 IFN-a-related non-hematologic toxicity, persisting for more than 1 month despite appropriate dose reductions and optimal medical management, with IFN-a administered at a dose of at least 25 MIU/m2/week. A documented > grade 3 IFN-α-related non-hematologic toxicity that is life- threatening such that retreatment with IFN-α would be deemed medically inappropriate is also considered Intolerance of Treatment. Under these conditions, treatment with IFN-a should be discontinued and the patient crossed over to the ST1571 arm. If such toxicity occurs after crossover to IFN + Cytarabine, the patient should be discontinued from the study.

3.8. Concomitant treatment

3.8.1 Hydroxyurea

The concurrent administration of hydroxyurea was initially permitted only during the first 3 months of study treatment to keep the WBC < 20.0×10^9/L. Amendment 1 revised the protocol to allow use of hydroxyurea for up to 6 months, to allow comparison with the published results of a study of interferon and cytarabine in CML by Guilhot et. al.[19]

3.8.2 Other Concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient were allowed, provided their use is documented in the patient records and on the concomitant medication and therapies CRF (includes blood transfusions for patients with low hemoglobin and with thrombocytopenia). The concomitant administration of investigation drugs other than STI 571 was NOT allowed. The concomitant use of chronic systemic corticosteroid therapy for longer than two weeks was not permitted.

Because of the possible risk of either reduced activity or enhanced toxicity of the concomitant medication and/or STI 571, drugs known to be metabolized by the same CYP450 isoenzymes as STI 571, should be used with caution. Special care has to he given to the concomitant use of paracetamol (acetaminophen, Tylenol) with STI 571. The use of leukopheresis and anagrelide will be permitted during the first month and the first three months of treatment, respectively.

Patients with WBC > 20.0 x 10'/L should receive allopurinol 300 mg administered by single oral daily dose beginning ideally 48-hours prior to study drug administration. If the WBC count stabilizes, allopurinol may be discontinued at the discretion of the investigator.

3.9. Crossover

3.9.1 Initial crossover rules

Crossover to the other treatment arm will occur under any of the following circumstances:

- Failure to demonstrate a complete hematologic response at 6 months
- Failure to achieve a major cytogenetic response at 12 months, Loss of complete hematologic response, provided that progression to accelerated or blastic phase did not occur,
- Intolerance of treatment, defined in (c) below:

3.9.2 Amended crossover rules

After the primary endpoint was changed to time to progression, the crossover rules were changed such that patients could be offered to switch to the alternative treatment arm if one of the following occurred:

- Loss of CHR
- Loss of MCR
- Increasing WBC count
- Failure to achieve a MCR or CHR at 12 months
- Intolerance of treatment

Reviewer comment: Excessive crossover could confound the results of the trial, especially for the survival endpoint. The FDA had extensive discussions with the sponsor regarding this issue, and the sponsor eventually agreed to modify the primary endpoint. Excessive numbers of patients censored for intolerance or failure to achieve a MCR could potentially confound results. 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. Excessive crossovers without progression would tend to make interpretation of ITT progression results difficult and tend to obscure the differences between treatments.

3.10. Removal from study:

For any patient discontinuing the study the reason will be recorded. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

1. adverse event(s}
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. unsatisfactory therapeutic effect
5. subject's condition no longer requires study treatment
6. protocol violation
7. subject withdrew consent
8. lost to follow-up
9. administrative problems
10. death

This information will be recorded on the Study Completion CRF page at any time a patient discontinues the study. When discontinuation of study occurs due to intolerance of treatment, the reason may best be captured as 1) adverse event, 2) abnormal laboratory value or 3) abnormal laboratory test procedure depending on the nature of the toxicity which led to treatment intolerance. At any time during the study patients will discontinue the study when progression to accelerated phase or blast crisis occur. In this case, the reason for discontinuation is best captured as 4) unsatisfactory therapeutic effect. In case discontinuation of study occurs as a result of the decision to proceed to transplantation, the reason will be 5) subject's condition no longer requires study treatment. Details regarding BMT will be recorded on a separate section of the CRF.

3.11. Follow-up/safety considerations

3.11.1 Clinic visits:

A physical examination and vital signs (including heart rate, blood pressure, and body temperature} will be performed during screening, monthly during the first 6 months of therapy, then every three months for the next 12 months, and every six months thereafter, and on the day of discontinuation of study drug. Measure performance status at screening, then monthly for the first 6 months, then 3 monthly for the next 12 months, thereafter every six months, and on the day of discontinuation of study drug. The ECOG Performance Status Scale will be used in this study. Weight and body surface area will be performed at screening and recorded on the CRF.

Patients must be evaluated at the study center monthly for the first 6 months, thereafter for all bone marrow assessments. After the first six months of therapy, evaluations were performed at 6-week intervals for up to 5 years after study start. Patients who continue on therapy after 5 years of study start will be followed for SAEs and survival only.

During the first month of therapy all evaluations should be performed within + 2 days of the day indicated on the Evaluation Schedule. For the following 5 months, all evaluations should be performed within + 4

days. Thereafter, all evaluations must be performed within + 1 week of the day indicated on the Evaluation Schedule.

Crossover to the alternative treatment arm does not constitute discontinuation of study. The reason for crossover and the assessments documenting it should be recorded on the CRF. After crossover, patients will continue to he monitored as per the visit schedule.

3.11.2 Laboratory assessments

Laboratory assessments should be performed at screening, weekly during weeks 1-5, every two weeks during weeks 5-17, at weeks 21 and 25, then every six weeks thereafter, and on the day of discontinuation of study treatment.

Whenever crossover to the alternative treatment arm occurs, hematology and biochemistry evaluations will be performed weekly during the first 4 weeks after switching treatment, every two weeks for the following 3 months and every 4 weeks for the next 2. The remainder of the evaluations should follow the original visit schedule.

Hematology includes assessment of hemoglobin, total WBC count, platelet count, and a differential count including neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, promyelocytes, myelocytes and metamyelocytes, and blast percentage. Additional hematology evaluation during the 10-day period of Cytarabine administration may be required, at the discretion of the investigator, in order to monitor neutropenia and thrombocytopenia. These data need to be recorded on the additional hematology CRF pages only if grade 3/4 toxicity occurs.

Biochemistry includes total bilirubin, total protein, albumin, LDH, AST (SGOT), ALT (SGPT), alkaline phosphatase, creatinine, BUN, urea, and uric acid.

Bone marrow analyses were to be performed during screening, every three months for the first 12 months of therapy, and every six months thereafter.

4 Efficacy Parameters

4.1. Initial Primary Efficacy Parameter: Time to Treatment Failure (TTF)

- Failure to achieve a complete hematologic response at 6 months, or
- Failure to achieve a major cytogenetic response at 24 months, or
- Loss of complete hematologic response, or
- Progression to accelerated or blastic phase of CML, or
- Intolerance of treatment, or
- Death

Reviewer comment: Time to Treatment Failure was not acceptable to the FDA as an endpoint for registration, since it is a composite of both efficacy and toxicity. This endpoint was subsequently amended.

4.2. Final primary objective: Progression Free Survival (PFS)

4.2.1 Definition of Progression (per Amendment 2 dated 11-1-00 p.9)

- Death
- Accelerated or blastic phase,
  - Accelerated phase is defined as the appearance of one of the following: blasts in the blood or bone marrow ≥ 15%, or percentage of blasts plus promyelocytes in the peripheral blood or bone marrow ≥ 30%, or peripheral basophils ≥ 20%, or thrombocytopenia ≤ 100 x 10'/L unrelated to therapy.
  - Blastic phase is defined as blasts in the blood or bone marrow ≥ 30% or appearance of extramedullary involvement (e.g. chloromas), except for liver and spleen.

- Loss of CHR was defined as the appearance of any of the following, confirmed by a second determination > 1 month later while under continuous treatment with maximum tolerated doses of the assigned study medication:
  - WBC count that rises to > 20 x 10^9L; or
  - Platelet count that rises to > 600 x 10^9/L
  - Progressing splenomegaly to a size > 5 cm below the left intercostal margin to be confirmed on two occasions at least 4 weeks apart
  - Appearance of > 5% myelocytes + metamyelocytes in the peripheral blood
  - Appearance of blasts or promyelocytes in the peripheral blood

- Loss of MCR, defined as an increase in the Ph + bone marrow cells by at least 30 percentage points (e.g., from 20% to 50%, or from 30% to 60%) confirmed by a second cytogenetic analysis > 1 month later

The primary efficacy parameter was defined as **progression free survival** (Section 3.5.3.1 of Amendment 2, p. 20). **Progression** was defined as one of the following events:

- Death
- Accelerated or blastic phase (as defined in section 3.5.3.2), or
- Loss of CHR (as defined in section 3.1)
- Increasing WBC count (as defined in section 3.1)
- Loss of MCR (as defined in section 3.1)

In section 6.3 of post text supplement 7 of amendment 2 (p. 10) Progression – free survival was defined as "includes the following events,"

- Progression to accelerated phase or blast crisis
- Increasing WBC count defined as a doubling of > 20.0 x 10'/L
- Loss of CHR (at any time)
- Loss of MCR (at any time)
- Death due to any cause

Reviewer comment: The definitions of accelerated and blastic phase are identical to those proposed by Kantarjian, *et. al.*, with the exception that cytogenetic clonal evolution was a criterion for accelerated phase in Kantarjian's system and was not part of the protocol 106

definition.[20] The requirement for splenomegaly was inconsistent and only found in the initial definition of progression in Section 3.5.3.1. of the protocol and not in the clinical study report data analysis section. The protocol referred both to time to progression (TTP) (Section 3.5.3.1 of Amendment 2) and to progression free survival as the primary efficacy endpoint. However, if deaths are treated as progressions, these endpoints are essentially equivalent. Presumably the statement in section 6.3 of post text supplement 7 of amendment 2 (p. 10) that PFS "includes the following events" was also a typographical error as PFS would include time that patients were free of the listed events. Although the definitions of progression were somewhat inconsistent, these inconsistencies were not judged likely to affect interpretation of overall results

4.2.2 Definition of progression for those not achieving a CHR

For patients not achieving a CHR, a hematological progression will be defined as a doubling of WBC count at least one month apart with at least the second value > 20 0 x 10'/L. Patients must be on continuous treatment with maximum tolerated doses of STI 571 or IFN-α combined with Cytarabine (or hydroxyurea administered within the first 6 months of start of therapy).

Reviewer comment: The definition of increasing WBC was inconsistent, sometimes referred to as a "count that rises to > 20 x 10^9/L," or "doubling of > 20.0 x 10^9/L " or in table 6.3 "No of Leukocytes above 20x 10^9/L." In the clinical study report data analysis section 6 2.1, an increase in WBC was counted as a progression "if approved by the SMC as reason for crossover." For the purposes of the FDA review, five WBC counts above 20.0 x 10^9/L were treated as evidence of progression.

5 Secondary Efficacy parameter definitions

5.1. Complete Hematologic Response (CHR)

All of the following must be present for > 4 weeks:

- Normalization of peripheral blood counts, i.e. WBC < 10.0 x 10^9/L and platelet count < 450 x 10^9/L.
- Normal WBC differential (no peripheral blood blasts and promyelocytes, a sum of myelocytes + metamyelocytes in the peripheral blood of < 5% will be permitted; more immature granulocytes will not be permitted)
- No evidence of disease-related symptoms or extramedullary disease, including spleen and liver

For the purpose of assessing CHR, hematology laboratory evaluations and physical examination to assess extramedullary disease, will be performed monthly for the first 6 months of therapy, then every 3 months for the next 12 months, every six months thereafter, and on the last day of treatment. If additional evaluations to assess CHR are performed the results should be captured on the CRF (additional CRF pages are provided). Any patients who achieve CHR before 6 months but are no longer in CHR or are treatment failures will be considered non-responders.

After a CHR has been confirmed as defined above, loss of complete hematologic response is defined as the appearance of any of the following, confirmed by a second determination > 1 month later:

- WBC count that rises to > 20.0 x10^9/L.
- Platelet count that rises to > 450 x 10^9/L.
- Appearance of extramedullary disease.
- Appearance of > 5% myelocytes + metamyelocytes in the peripheral blood.
- Appearance of blasts or promyelocytes in the peripheral blood.

Duration of CHR is defined as the time from the first documentation of the complete hematologic response to the date the loss of complete hematologic response or treatment failure is documented, whichever occurs first.

5.2. Cytogenetic Response

Cytogenetic analyses were performed every three months for the first 12 months of therapy and every six months thereafter, and on the last day of treatment. A minimum of 20 metaphases must be examined in each bone marrow sample, whenever possible. Cytogenetic analysis results must be documented on the CRF. Cytogenetic response was defined as follows in terms of the percentage of Ph chromosome-positive metaphases in bone marrow:

- Complete cytogenetic response (CCyR) (if patients had 0% Ph+ cells at least once).
- Partial cytogenetic response (PCyR) (if patients had ≤ 35% Ph+ cells at least once).
- Minor cytogenetic response (PCyR) (if patients had ≤ 65% Ph+ cells at least once).
- Minimal cytogenetic response (PCyR) (if patients had ≤ 95% Ph+ cells at least once).
- No response (on study) (if patients never had a minimal cytogenetic response and were still on treatment).
- Loss of cytogenetic response is defined as an increase in the Ph+ bone marrow cells by at least 30 percentage points (e.g., from 20°/o to 50% or from 30% to 60%) confirmed by a second cytogenetic analysis > 1 month later.
- No response (off study) (if patients never had a minimal cytogenetic response and crossed over or discontinued for reasons other than progression or death).
- No response (progressive disease/death) (if patients never had a minimal cytogenetic response and crossed over or discontinued for progression or death).
- Philadelphia negative at baseline (patients who had no documentation of Ph+ at baseline; for ITT analyses only, these patients are excluded from per protocol analyses).

5.3. Major Cytogenetic Response (MCyR)

Major cytogenetic response (McyR) was defined as the sum of:

- Complete cytogenetic response (CCyR) (if patients had 0% Ph+ cells at least once), and
- Partial cytogenetic response (PCyR) (if patients had ≤ 35% Ph+ cells at least once).

5.4. Duration of major cytogenetic response

Duration of major cytogenetic response is defined as the time from the first documentation of the response to the date the loss of cytogenetic response or treatment failure is documented, whichever occurs first.

5.5. Survival

In order to evaluate overall survival all patients will be followed every three months after discontinuation of study treatment until all patients have either died or been lost to follow-up, or for up to 8 years. A separate Survival Information Case Report Form will collect this information. It will also be collected whether the patient underwent bone marrow transplant and the date of the transplant

5.6. Quality of Life parameters

5.6.1 FACT-BRM

The instrument used to measure quality of life was the Functional Assessment of Cancer Therapy biologic response modifier (FACT-BRM) questionnaire, consisting of a general quality of life instrument and several treatment-specific modules. The general domains covered by the instrument include physical well being, functional well being, social well being and emotional well being. In addition two treatment-specific domains were included, and were designed to assess the impact of biological response modifiers (BRM) on physical and emotional functioning. A quality of life assessment was performed in patients at baseline, at monthly intervals for the first six months of therapy then at the end of 9, 12, 18 and 24 months. Additionally, an assessment was to be performed whenever crossover to the other treatment arm occurs. The questionnaire as to be completed for all patients discontinuing study treatment before 2 years of study start.

5.7. Drug levels and pharmacokinetic assessments

A population pharmacokinetic study will be performed using a sparse sampling technique for all patients on the STI 571 treatment arm. Pharmacokinetic sampling will be performed on Day 1 and Day 29 of therapy. On each of these days, three samples will be taken. The sample times may depend on the patient's convenience, but should be drawn between 1 and 3 h and between 6 and 9h after STI 571 administration and before taking the capsule of the following day, either day 2 or day 30. A one-compartment model with first-order absorption and a linear pharmacokinetics will be employed as the kinetic model for a nonlinear mixed effect model to investigate the effect of the population characteristics like age, weight, creatinine, SGOT and SGPT on the model parameters.

5.8. Pharmacogenomic assessments

Pharmacogenomic studies will he conducted to permit the potential identification of genetic factors related to leukemia that may predict response to treatment with STI 571 and/or predict the patient's relative susceptibility to drug-drug interactions or serious side effects. Information from this study will not be used to change the diagnosis or therapy of the patient.

Advances in the understanding of the molecular basis of leukemia and malignant processes provide an important new opportunity to investigate the influence of genetic variation on drug effects and gene function. It is planned to study polymorphisms m genes in blood cells that are linked to the etiology of leukemia, those related to the drug target(s), bcr-abl and c-Kit and those in drug metabolism genes (e.g. CYP3A4). New genetic information is being accumulated continually. As a consequence, it is not possible to enumerate all of the polymorphisms that will be assayed at this time. Furthermore, it is purposed to study RNA expression using microarray technology before and 24 hours after the first dose of STI 571 in a subset of 12 patients to study the in vivo effects of STI on gene expression. Additionally, in the same 12 patients, we plan to assay bone marrow cells before the first dose of STI 571 in order to compare the gene expression profiles in blood and bone marrow.

Assessment schedule: On the first day of study before study treatment administration, 20 ml of blood will be obtained in all patients enrolled in the US only (approximately half of the patients). In 12 patients enrolled in US sites and receiving STI 571 as initial therapy, an additional 20 ml of blood will be drawn 24 hours after the first dose. In these same patients, 5ml of bone marrow aspirate will be collected at screening.

6 Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry, regular measurement of vital signs and the performance of physical examinations, and documentation of all concomitant medication and therapies.

6.1. Clinic Visits

A physical examination and vital signs (including heart rate, blood pressure, and body temperature} will be performed during screening, monthly during the first 6 months of therapy, then every three months for the next 12 months, and every six months thereafter, and on the day of discontinuation of study drug.

Weight and body surface area will be performed at screening and recorded on the CRF.

Performance status was measured at screening, then monthly for the first 6 months, then 3 monthly for the next 12 months, thereafter every six months, and on the day of discontinuation of study drug. The ECOG Performance Status Scale was used in this study.

6.2. Laboratory assessments

6.2.1 Schedule

Laboratory assessments were to be performed at screening, weekly during weeks 1-5, every two weeks during weeks 5-17, at weeks 21 and 25, then every six weeks thereafter, and on the day of discontinuation of study treatment.

Whenever crossover to the alternative treatment arm occurs, hematology and biochemistry evaluations were to be performed weekly during the first 4 weeks after switching treatment, every two weeks for the following 3 months and every 4 weeks for the next 2. The remainder of the evaluations should follow the original visit schedule.

6.2.2 Hematology

Hematology includes assessment of hemoglobin, total WBC count, platelet count, and a differential count including neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, promyelocytes, myelocytes and metamyelocytes, and blast percentage. Additional hematology evaluation during the 10-day period of Cytarabine administration may be required, at the discretion of the investigator, in order to monitor neutropenia and thrombocytopenia. These data need to be recorded on the additional hematology CRF pages only if grade 3/4 toxicity occurs.

6.2.3 Biochemistry

Biochemistry includes total bilirubin, total protein, albumin, LDH, AST (SGOT), ALT (SGPT), alkaline phosphatase, creatinine, BUN, urea, and uric acid.

6.2.4 Bone marrow analysis

Bone marrow analysis will be performed during screening, then every three months for the first 12 months of therapy and every six months thereafter.

6.3. Endpoints: safety data

6.3.1 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, were collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment. Adverse events occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

As far as possible, each adverse event will also be described by 1. its duration (start and end dates), 2. The NCI/NIH Common Toxicity Criteria severity grades 1 – 4 (Post-text supplement. 1). 3. Its relationship to the study drug (suspected / not suspected), 4. The action(s) taken and, as relevant, the outcome.

Examples of the severity grade, relationship to study drug and actions taken, as presented in the case report form are provided in Section 9.1.3. Instructions for completing Adverse Event Case Report Forms.

6.3.2 Serious adverse events

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety each serious adverse event must also be reported to Novartis within

24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which: 1. is fatal or life-threatening 2. Required or prolonged hospi1alization 3. Was significantly or permanently disabling or incapacitating 4. Constitutes a congenital anomaly or a birth defect 5. Are medically significant, may jeopardize the subject and may require medical or surgical

Events not considered to be serious adverse events are hospitalizations for the routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen, or treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities

7 Statistical and analytic considerations:

7.1. Sample size estimates

Time to treatment failure was the initial primary efficacy objective. As a result of Amendment 2 dated 11/2/00, progression free survival became the amended primary objective. Amended sample size estimates employed an 80% power to detect a relative hazard ratio of 0.75 for the STI 571 arm relative to the INF+Cytarabine arm by two-tailed log rank analysis. This corresponds to an increase in the 5-year progression free survival rate from 50% in the IFN-α +Cytarabine arm to approximately 60% in the STI 571 arm. A median follow up time of 5.25 years and an accrual time of 0.5 years with a uniform patient entry were assumed. The total observation period is expected to be 5.5 years. Under these assumptions, approximately 822 patients should be randomized to obtain the required 385 events. The required 385 events are expected to have occurred after 5.5 years. However, the analysis will be conducted at whatever time point the required number of events are reached. To account for a yearly 10% dropout rate a total of 1032 patients will be recruited.

Primary Analysis plan: Kaplan-Meier estimates will be provided for progression-free-survival. Patients who are lost to follow-up (withdrew consent) are censored at the time they discontinue treatment. Patients who are still receiving treatment without showing an event are censored at the time of last examination. For the first line efficacy analysis, patients who show intolerance before the endpoint was reached are censored at the time they crossover to the alternative treatment arm.

7.2. Interim Analysis

An analysis was planned 6 months after the last patient was enrolled based on the 6-month CHR rate and QOL endpoints. This was subsequently amended to an analysis of the Major Cytogenetic Response (MCR) rate 12 months after the last patient was enrolled. Using a two-sided test with a 5% significance level and power of 80%, with the sample size estimated for the primary efficacy endpoint it will he possible to detect at least a 10% increase in the rate on the

STI517 arm as compared to the expected 41% rate on the IFN-a +Cytarabine arm. The expected 12-month MCR rate was based on the results in patients treated with IFN-α +Cytarabine published by Guilhot et al. An Independent Data Monitoring Board was to evaluate the results of the 1-year MCR rate analysis, as well as safety and efficacy data on an ongoing basis.

7.3. Complete hematological response

This analysis (for ITT and PP) will be carried out 6 months after the last patient was enrolled. A CHR will be counted regardless whether it was achieved under the original dose or after dose escalation as per protocol. CHR will only be included when it occurs or is sustained at 6 months, i.e. any patients who achieve CHR before 6 months but are no longer in CHR or are treatment failure will be considered non-responders.

Furthermore, the one-sided 95% confidence interval for the difference between CHR rates is calculated using normal approximation and assuming equal variances. In case there is evidence of superiority of the on the STI 571 arm, CHR the exact probability will be tested by unadjusted logistic regression analysis.

The 6-month CHR rates achieved in the two treatment groups will be compared by logistic regression analysis taking into account either the Sokal or the Hasford score. Duration of complete hematologic response is only defined for patients who achieved complete hematologic response.

7.4. Major Cytogenetic Response

The major cytogenetic response rate (MCR) will be compared between the two treatment groups by logistic regression analysis taking into account the Sokal score (for ITT and PP). Duration of major cytogenetic response is only defined for patients who achieved major cytogenetic response. For duration of MCR and CHR, the treatment groups are compared using the log-rank test and Cox' regression taking into account either the Sokal or Hasford score.

The FDA reminded the sponsor (Pre NDA meeting, 4/17/02) that unconfirmed cytogenetic responses should not be counted. If an individual has a CCyR on one occasion and a PCyR on a second evaluation it will be scored as a PCyR. If the order is reversed and no subsequent study is done it is still a PCyR.

7.5. Survival

Survival times will be calculated regardless of crossover as follows: Survival time (days) = date of death – randomization date + 1. Patients who are still on follow-up at the time of survival analysis will be censored at the last date of contact. The survival time and response duration is presented as Kaplan-Meier curves.

7.6. Intolerance of treatment

The number of patients crossing over to the alternative treatment arm due to intolerance to treatment will be summarized by presenting the rate with the 95% confidence intervals in each treatment group.

7.7. Safety evaluation

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event will be summarized by severity and relatedness to study medication for each treatment group. Laboratory data will be summarized using the NCI/NIH common toxicity criteria. Safety data will be summarized before and after crossover.

7.8. QOL endpoints

Quality of Life of patients was assessed by the "FACT-BRM," a questionnaire patient reported outcomes instrument which "focuses on the impact of interferon-related toxicities on the functional and cognitive assessment of the patient," according to the protocol. The Functional Assessment of Cancer Therapy Biologic Response Modifier (FACT-BRM) questionnaire consisted of a general "quality of life instrument" and two "treatment-specific modules" (the Biologic Response Modifier or BRM component). Symptom assessment was performed at baseline, at monthly intervals for the first six months of therapy, and then at the end of 9, 12, 18 and 24 months. The primary QoL endpoint was the treatment outcome index (TOI) consisting of

- the physical and functional subscales of the FACT BRM
- 2 BRM "treatment specific" subscales.

The primary analysis will examine the time from baseline to six months post-randomization. A repeated measurement analysis will be performed using all available data and baseline data as a covariate. In case the withdrawal rate is non- neglectable, a sensitivity analysis integrating alternative modeling will assess the treatment effect. A reliable estimate of the target improvement in QoL in the experimental arm as compared to the control arm is difficult to make as the published experience of commonly used QoL instruments including FACT-BRM does not comprise patients with early chronic phase CML. However, a sub-study will be conducted to estimate the average change and effect sizes of FACT-BRM measures using the GRC Scale questionnaire. Additionally, based on the FACT-RRM physical subscale with a score ranging from 0 (best) to 28 (worst) and assuming a baseline score of 20 in the control arm, the planned sample size for this trial enables the detection of a treatment difference of as low as 1.2, with 80% power and 5% alpha.

A secondary analysis will be conducted using patient data from baseline through two years, in order to analyze group differences in quality of life trajectories over time using a multilevel or growth curve model. This model describes each patient's QOL trajectory over time via a patient-specific model. The coefficients that describe each patient's latent growth trajectory are then modeled as a function of between-patient variables, such as treatment group, age, severity level, etc.

8 Amendments to protocol: (Three)

8.1. Amendment 1: (dated 24 July, 2000)

Concomitant use of hydroxyurea (HU) to keep the WBC < 20.0 x 10'/ was extended from the initial 3 months of treatment allowed to 6 months of therapy, to provide comparability to a study by Guilhot et al.

Based on a preliminary study of the effect of food on the bioavailability of STI 571 it was recommended that STI 571 be administered immediately before or during meals.

Phase 1 data suggested a significant incidence of grade 3 thrombocytopenia in CML patients in chronic phase treated at doses > 750 mg/daily, therefore the protocol was changed to allow dose escalation of STI 571 to be performed step wise from 400 mg qd to 600 mg qd and to 400 mg bid.

The dose reduction schema for patients on the STI 571 treatment arm was adapted to permit to re-escalate the dose to the starting dose level in the absence of recurrent toxicity or additional toxicity(ies). Further, the dose modification guidelines in both treatment arms are adjusted with the aim of maintaining patients under the original treatment for as long as clinically manageable.

The protocol was changed to allow the inclusion of patients with variant of (9:22) chromosomal translocations.

A requirement for PCR testing to follow-up molecular response in all patients who achieve a complete cytogenetic response was added to the protocol, as a secondary endpoint.

Fluid retention was identified as a common finding in all studies. This can manifest as subcutaneous edema at any site, including the ankles and pretibial tissues. Some patients have developed pleural effusions and/or ascites, whilst others have had considerable weight. As a result of these findings, monitoring of body weight during the course of the study was added to the trial evaluations.

Guidance regarding the use of selected drugs with potential for drug interaction with STI 571 was included in this amendment.

8.2. Amendment 2: (dated Nov 1, 2000)

As a result of discussion with the FDA regarding the unacceptability of the initial primary endpoint of time to treatment failure (TTF) and to provide the necessary requirements of a registration study in this patient population, the primary endpoint was changed to progression free survival.

Progression was defined as:

- Accelerated phase, blast crisis, death
- Loss of CHR or MCR

• Increasing WBC counts in patients who did not achieve CHR

As a consequence of the change in the primary endpoint, the crossover rules have also been altered. Patients may be offered to switch to the alternative treatment arm if one of the following occurs:

• Loss of CHR
• Loss of MCR
• Increasing WBC count (The Study Management Committee must approve all situations of treatment crossover due to increasing WBC count)
• Failure to achieve a MCR or a CHR at 24 months
• Intolerance of treatment

• Patients who switch to the alternative treatment arm due to failure to achieve a MCR at 24 months or treatment intolerance will be censored for observation for the primary endpoint analysis, at the time of crossover.

The initial proposed interim analysis of 6-month CHR rate and quality of life was changed to the Rate of Major Cytogenetic Response (McyR) at 12 months. Activity will be demonstrated if the 12-month MCyR rate in the experimental arm is superior to the rate in the control arm.

All patients enrolled in the study prior to approval of amendment 2 must be re-consented because of changes in the crossover rules.

If a patient is crossed over to the alternative treatment arm before progression, progression free survival will be censored at the date of crossover, this includes patients who did not re-consent following amendment 2 and the event leading to the crossover does not meet the definition of progression.

The Study Management Committee (SMC) was required to review all requests for crossover due to intolerance of treatment. Based on these activities, the protocol was changed to incorporate guidelines to manage the requests with regard to the strict adherence to protocol in dose reduction for non-hematological toxicity.

The protocol was changed to provide detailed guidance regarding the dose escalation of interferon during the initial 4 weeks of treatment.

To ensure consistency with the guidelines used for dose escalation of Cytarabine in the IFN-c+ Cytarabine treatment arm, the condition under which dose escalation of STI 571 was permitted i.e. failure to achieve MCR at 12 months was changed to failure to achieve at least a minor cytogenetic response at 12 months.

Patients who progress to accelerated phase or blast crisis whilst under protocol treatment with IFN+ Cytarabine may be offered treatment with STI 571 at a dose of 600mg once daily. These patients will be treated according to the extension protocol. (Extension I to protocol CSTI 571 0106)

Patients who received previous treatment with anagrelide may be eligible for this study.

Patients will be eligible on anti-coagulant therapy with INR > 1.5 ULN.

In patients with a calculated body surface area > 2.0m' it is recommended to use ideal body weight when calculating the total daily dose of INF-c.

In order to calculate either Sokal or Hasford score the hematology (including differential) and spleen size at the time of initial diagnosis with CML will be recorded in the case report form .

A manual WBC count differential is required at visits where the patient attends for bone marrow examination.

8.3. Amendment 3: (dated January 23, 2002)

The interim analysis of this study showed early evidence of superiority of the STI 571 treatment with regards to the primary endpoint of study, i.e. time-to-progression, as well as all other efficacy endpoints considered in this analysis: time to accelerated phase or blast crisis, rate of complete hematologic response. and rate of major cytogenetic response (MCR). Considering these results, several changes of the protocol were implemented:

Patients in the IFN – Cytarabine arm who had achieved a MCR were encouraged to continue with the assigned therapy as long as tolerated. Patients were informed about the new data, emphasizing the short follow-up currently available. If these patients wished to switch to STI 571 they were offered the opportunity to do so. Patients who had not achieved a complete hematologic response (CHR) or a MCR with IFN – Cytarabine after one year on treatment) were offered the possibility to cross over to STI 571 treatment after 12 months (and not 24 months as written in the original protocol).

9 Study Results

9.1. Study Population

Between 16th June 2000 and 30th January 2001, a total of 1106 patients were enrolled and randomized, 553 in each arm. These patients were randomized at 177 centers in 16 countries.

9.2. Analysis populations

The following analysis populations were defined in the protocol:

Intent To Treat population consisted of all randomized patients (n = 1106, with n = 553 in each treatment arm). The ITT analysis of cytogenetic response excluded any patient with the major violation of no documentation of Ph+ as ' Ph- at baseline'.

Safety population: all patients who received at least one dose of study medication (n = 1084, n = 551 on STI 571 and n = 533 on IFN + Ara- C).

Per- protocol (PP) population: all patients with untreated Ph+ chronic phase CML who received at least one dose of study medication. Any patient who received prohibited anti-neoplastics while on study medication was excluded. The protocol stated that patients without 2 post- baseline assessments and those who crossed over without fulfilling protocol criteria were also to be excluded from PP analyses.

The numbers of patients in the different analysis populations are summarized in the table below:

Table 6: Numbers (%) of patients in analysis populations by treatment group

Patient population	Gleevec N=553 (%)	IFN+Cytarabine N=553(%)	All randomized N=1106 (%)
ITT population	553 (100)	553 (100)	1106 (100)
Safety population	551 (99.6)	533 (96.4)	1084 (98.0)
Per-protocol population	542 (98.0)	524 (94.8)	1066 (96.4)

Approximately 2% of the ITT patients were not included in the safety and 5% were not included in the per protocol populations. More patients on the interferon treatment arm were excluded from the safety and per protocol populations, compared with patients on the Gleevec arm.

9.3. Patient Demographics

Table 7 Demographic and background Characteristics

	Gleevec (n=553)	IFN+Cytarabine (n=553)
Sex		
Men	342 (61.8%)	310 (56.1%)
Women	211 (38.2%)	243 (43.9%)
Age (years)		
Median	50.0	51.0
Range	18-70	18-70
< 40	141 (25.5%)	128 (23.1%)
≥ 40 - < 50	115 (20.8%)	120 (21.7%)
≥ 50 - < 60	183 (33.1%)	177 (32.0%)
≥ 60	114 (20.6%)	128 (23.1%)
Race		
Caucasian	494 (89.3%)	500 (90.4%)
Black	28 (5.1%)	24 (4.3%)
Asian	12 (2.2%)	6 (1.1%)
Other	19 (3.4%)	23 (4.2%)
Weight (kg)		
N	540	539
Median	78.7	77
Range	40.0-169.5	41.0-157.7
Body surface area (m^2)		
N	508	526
Median	1.91	1.88
Range	1.06-2.89	1.29-2.67
ECOG Performance Status		
Missing	5 (0.9%)	12 (2.2%)
Grade 0	425 (76.9%)	409 (74.0%)
Grade 1	115 (20.8%)	121 (21.9%)
Grade 2	8 (1.4%)	11 (2.0%)

The study population demographics were fairly well balanced between treatment groups. Slightly more women and patients over 60 years old were accrued to the interferon arm, and the interferon patients had slightly worse performance status, but the differences were small. Approximately 60% of patients accrued were male, this reflects the incidence of the disease in the general population. Ninety percent of patients accrued were Caucasian.

9.4. Prognostic characteristics

Sokal proposed a prognostic model for CML using age, spleen size, and the presence of circulating blasts in the peripheral blood based on the results of a multivariate regression analysis of factors correlated with survival in 813 CML patients. [21] Hasford, *et. al.* subsequently developed a more comprehensive prognostic scoring system based on age, spleen size, blast count, platelet count, eosinophil count, and basophil count.[22] Patients are divided into low, intermediate, and high-risk groups in terms of their expected survival. At study entry, 70% percent of patients could have their Sokal risk determined and 69% could have their Hasford risk determined. The patients in the two treatment arms were well balanced with respect to both the Hasford and the Sokal prognostic models. Prognostic characteristics for those patients whose risk could be determined at diagnosis are summarized in Table 5:

Table 8: Sokal and Hasford Scores at diagnosis

	GLEEVEC N=553 (%)	IFN+Cytarabine N=553 (%)	All Randomized N=1106 (%)
Sokal risk determined	383 (69.2)	394 (71.2)	777 (70.3)
Low	201 (52.5)	190 (48.2)	391 (50.4)
Intermediate	111 (29 0)	116 (29.6)	227 (29.3)
High	71 (18.5)	88 (22.4)	159 (20.5)
Hasford risk determined	374 (67.6)	387 (70 0)	761 (68.8)
Low	170 (45.5)	173 (44.9)	343 (45.1)
Intermediate	166 (44.4)	176 (45.6)	342 (44.9)
High	38 (10.2)	38 (9.9)	76 (10.0)

The Sokal and Hasford CML prognostic scores appeared to be well balanced between treatment arms for those patients whose scores could be determined at diagnosis.

Since not all patients could be scored for prognosis at diagnosis, the FDA determined the number of patients in each arm at study entry with adverse prognostic characteristics of age over 50 years, the presence of blasts in the peripheral blood at baseline, spleen size over 3 cm, and basophils over 3%. These characteristics are based on the Hasford prognostic model. The results are presented in Table 6.

Table 9: Number of patients with adverse prognostic characteristic by treatment

Characteristic	Gleevec	Interferon	total
Any blasts in peripheral blood	104	102	206
Spleen size > 3 cm	87	85	171
Basophils > 3%	231	264	495
Platelets > 1500/μl	4	6	10
Age > 50	275	289	564

The two treatment arms appeared to be fairly well-balanced with respect to these known adverse prognostic characteristics, except that the interferon had slightly more patients over the age of 50 and more patients with basophils > 3%. The Fisher's exact test p-value for Basophils > 3% is 0.053 (chi-square p-value is 0.046). None of the other factors were significantly different between arms.

9.5. Other disease characteristics

Table 10 illustrates some baseline disease characteristics of the patients accrued.

Table 10: Baseline disease characteristics

	Gleevec (n=553)	IFN+Cytarabine (n=553)
Previous hydroxyurea treatment?		
No	68 (12.3%)	81 (14.6%)
Yes	485 (87.7%)	472 (85.4%)
Time since diagnosis (months)		
Median	2.14	1.77
Interquartile range	1.0-3.7	0.8-3.2
Range		

Disease characteristics appeared fairly well balanced in terms of time between diagnosis and study entry as well as for previous hydroxyurea treatment. Slightly more patients had been previously treated with hydroxyurea and the median time since diagnosis were lightly longer in the Gleevec treatment group.

9.6. Conclusions

Slightly more women and patients over 60 years old were accrued to the interferon arm, and the interferon patients had slightly worse performance status, but the differences were small. Approximately 60% of patients accrued were male, however this reflects the incidence of the disease in the general population. Ninety percent of patients accrued were Caucasian. The Sokal and Hasford CML prognostic scores appeared to be well balanced for those patients whose scores could be determined at diagnosis. The two treatment arms appeared to be fairly well-balanced at study entry with respect to known adverse prognostic characteristics, except that the interferon arm had significantly more patients with basophils over 3%. Overall there were very small imbalances between treatment arms favoring the Gleevec treatment arm.

10 Study conduct

10.1. Protocol Deviations and violations

The sponsor reported 48 major protocol violations leading to exclusion from per protocol population. Major protocol violations are summarized in the table below.

Table 11: Major protocol violations leading to exclusion from PP population

Description	Gleevec	IFN
Discontinuation after randomization without receiving study drug	2	20
No Ph chromosome positivity	3	4
No confirmation of chronic phase CML (Pt in AP or BC)	7	12
Total	12	36
Listed in the datasets as not per protocol	11	29

Two percent of patients on the Gleevec arm and five percent of patients on the interferon arm were excluded from the per protocol analysis for major protocol violations. Most of these were patients randomized to Interferon who went off the study prior to receiving the study drug. Seven patients had no confirmation of Philadelphia chromosome positivity. Nineteen patients were found to be in accelerated phase or blast crisis and therefore had no confirmation of chronic phase: 12 on the interferon arm and 7 on Gleevec. The results of these analyses are summarized below:

Table 12: Patients in accelerated phase at entry

Analysis	Gleevec	IFN
Novartis	7	12
FDA	7	8

The sponsor's analysis of patients in accelerated phase at entry found more patients in accelerated phase on the interferon arm but the FDA found approximately equal numbers of patients in both arms in accelerated phase. The most common major protocol violation was discontinuation from the study following randomization without receiving the study drug, which occurred in 20 patients on the interferon arm and in only 2 patients on the Gleevec arm. The reasons patients withdrew prior to receiving the study drug are summarized in the table below:

Table 13: Patients who withdrew prior to receiving first treatment

	GLEEVEC N=553 (%)	IFN+Cytarabine N=553 (%)
No. of patients withdrew prior to beginning treatment	2	20
Reason for discontinuation	None Given	
Bone Marrow Transplant		1
Protocol Violation		4
Withdrew consent		14
Administrative Problems		1

The most common reason for withdrawing from the study was withdrawal of consent, which occurred in 14 patients on the interferon arm and in no patients on the Gleevec arm. Minor protocol violations included history of previous cancers, besides superficial skin cancers; abnormal laboratory parameters, and greater than 6 months between randomization and diagnosis. Minor protocol violations did not result in exclusion from the per protocol population, and are summarized in the table below:

Table 14: Minor Protocol Violations (deviations)

Description	Number of patients
History of previous cancer (not active)	6
Laboratory parameter exceeds 1.5 x ULN	26
Received methotrexate (rheumatologic indication)	2
No Bone marrow aspirate within 4 wks of study enrollment	11
Diagnosis > 6 months prior to study entry	16

Conclusions: Two percent of patients on the Gleevec arm and five percent of patients on the interferon arm were excluded from the per protocol analysis because of major protocol violations. The most common major protocol violation was going off study without receiving the study drug. Most of these were patients randomized to interferon who withdrew consent prior to receiving the study drug. The next most common reason for a major protocol violation was the diagnosis of accelerated phase or blast crisis at study entry.

10.2. Study Discontinuations

The reasons for study discontinuation are summarized in the table below:

Table 15: Reasons for study discontinuation

Reason	Gleevec	Interferon	Total
Adverse Event	12	36	48
Unsatisfactory Therapeutic Effect	11	37	48
Bone Marrow Transplant	5	9	14
Protocol Violation	10	15	25
Withdrew Consent	10	75	85
Lost to follow-up	2	6	8
Administrative problems	0	7	7
Death	4	2	6

The most common reason patients were discontinued from the study was withdrawal of consent, which occurred in 5 times as many patients on interferon as on Gleevec. Adverse events and unsatisfactory therapeutic effect were the next most common reasons for study discontinuation, and were three times as common in the interferon arm as on the Gleevec arm.

10.3. Treatments received

Table 13 summarizes the study treatments received by patients on the two study arms:

Table 16 Treatments received in study 106

	Gleevec N=551 (%)	**IFN+Cytarabine N=553 (%)**
No. of patients without change of initial dose	304 (55.2)	68 (12.8)
No. of patients with change of initial dose	247 (44.8)	465 (87.2)
Change of initial dose		
Patients with interruptions >5 days	155 (28 1)	289 (54.2)
Patients with dose reductions	182 (33.0)	403 (75.6)
Patients with dose escalations*	36 (6.5)	0
Reason for dose change		
AE or laboratory abnormality	181 (32.8)	434 (81.4)
Lack of efficacy	18 (3.3)	1 (0.2)
AE or laboratory abnormality and lack of efficacy	14 (2.5)	1 (0.2)
Other	34 (6.2)	29 (5.4)

* only used for Gleevec when dose was >400 mg

Approximately half the patients on Gleevec were able to complete the study without a change of dose, and only twelve percent of the patients on interferon were able to complete the study without a change in dose.

10.3.1 Gleevec doses received

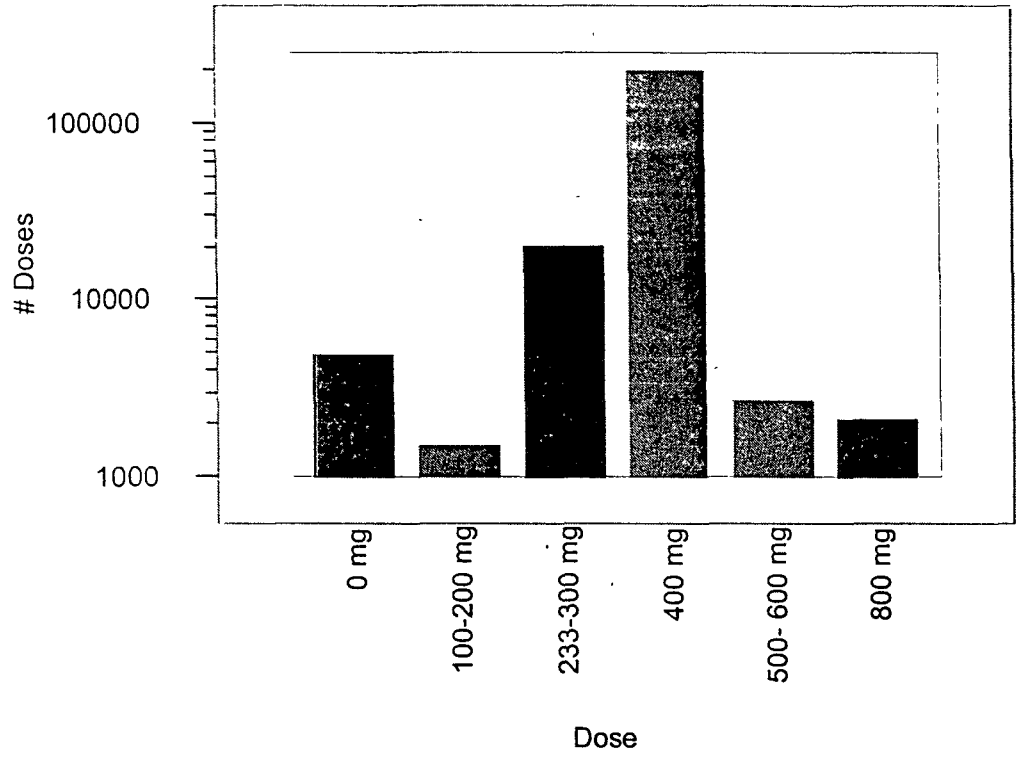
The following table lists the Gleevec dose levels given during the trial, and the percent of all Gleevec doses given by each dose level:

Table 17: Gleevec doses received during study 106

Dose (mg)	Dose held	100-200	233-300	400	500-600	800
# days	5017	1555	20585	201220	2771	2170
% of total	2.15%	0.67%	8.8%	86 2%	1.2%	0.93%

Eighty six percent of the Gleevec doses given were at the recommended starting dose level of 400 mg per day. 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. Figure 2 displays the Gleevec doses received on a logarithmic scale (total number of days on a given dose level) as of the data cutoff:

Figure 2: Doses of Gleevec received



The mean dose of Gleevec received by patients on the Gleevec arm of the study was 386 mg/day, for an overall dose intensity of 97% in patients on the Gleevec arm.

10.3.2 Interferon doses received

The protocol specified an interferon dose escalation goal over 4 weeks to a maximum target dose of 5 MU/m2/day. Out of 553 patients randomized to receive interferon, 533 (96.3%) actually received any recorded interferon doses. The following table summarizes the interferon doses received by those patients who actually received IFN. The median daily dose received was 4.9

MU/ day, which corresponds to 2.6 MU/ m2/ day for the IFN group, which had a median BSA of 1.89 m^2.

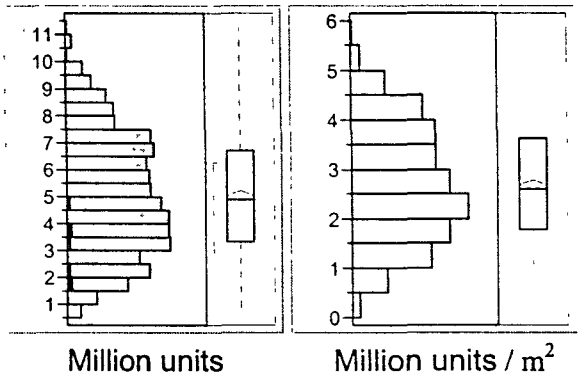
Table 18: Interferon doses received

	Million units	Million units/m2
N	533	513*
Mean	5.04	2.69
Median	4.89	2.60
% of Target dose	56	

* 20 patients did not have BSA recorded

The FDA estimated that the average dose delivered would have been 4.6 MU/m2 had each patient been escalated to the maximum dose on the schedule specified by the protocol. Therefore the overall dose intensity received by the interferon group compared with the target dose was approximately 56%. Figure 1 shows the distribution of median daily interferon doses over the study period:

Figure 3: Median daily Interferon doses MU/ and MU/ m^2



The dose intensity of interferon in the active control arm was 56% of the protocol-specified target dose. This compares with 68% – 78% of target dose intensity, which was received by patients on the interferon, and Cytarabine arm of the Italian CML study of interferon plus or minus cytarabine, which had an identical dose-escalation plan. The median doses were also 10% lower than those reported in the French CML study: 4.9 million units/day as compared with 5.4 million units per day. Body surface area was not reported in the French study.

10.3.3 Cytarabine doses received

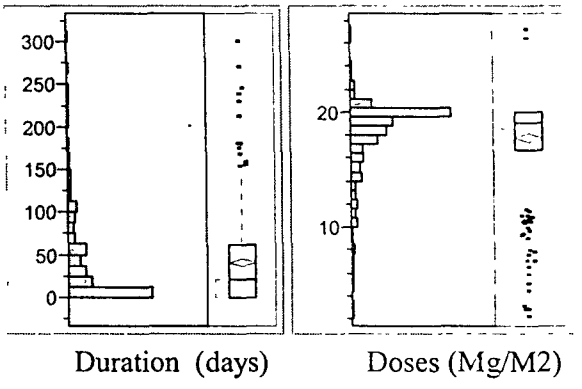
The protocol specified that, once the maximum tolerated dose of IFN-a is achieved, cytarabine was to be added at a dose of 20 mg/m /day (maximum daily dose of 40 mg) for 10 days every month, administered once a day subcutaneously. The following table summarizes the doses of cytarabine received in the population randomized to receive interferon.

Table 19 Cytarabine (Cytarabine) treatment received: Median Duration and dose

Group	N	Median duration of treatment as % of IFN	Median daily dose	
			mg	Mg/m2
Protocol specified	553	33 %	20	20
Pts receiving Cytarabine	374	18 %	35.9	19
All pts receiving IFN	533	11 %	35.9	17

Of 540 patients who actually received interferon, 375 (70%) received any cytarabine doses. The distribution of treatment duration with cytarabine and the median doses received in patients who received interferon are displayed in Figure 2 below:

Figure 4: Distribution of duration and median dose of Cytarabine doses received



10.3.4 Conclusions

Twenty eight percent of all patients required dose interruption of their Gleevec for over 5 days compared with 54% of patients on interferon. Thirty three percent of patients on Gleevec eventually required a dose reduction, and six percent required dose escalation (2% of total Gleevec doses given). The sponsor reported that three quarters of the patients on interferon required dose reduction and no patients were dose escalated during first line treatment. Dose reductions and interruptions were more frequently undertaken in the group treated with IFN + cytarabine than in those treated with Gleevec. The principal cause for dose modification in the former group being the occurrence of AEs or laboratory abnormalities. 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.

In comparison with published studies of interferon and cytarabine in CML, the dose intensity of interferon achieved on the active control arm in study 106 was slightly lower than the 70% interferon dose intensity obtained in the combination arm of an Italian study with a similar dose escalation plan.[23] The mean dose of 5.04 MU/day in study 106 also appeared to be slightly lower

than the mean daily dose of 5.4 MU/day in a similar French study.[24] The mean dose of cytarabine received appeared to be similar to that achieved in the French study, however only 70% of patients on interferon in the Gleevec study actually received cytarabine, as compared with 95% in the first 3 months of the Italian study. Overall the dose intensity of the active control arm appeared to be less than that achieved in published studies of interferon and cytarabine and was much lower than the dose intensity achieved in patients on the Gleevec arm. Seventy percent of patients on interferon in the Gleevec study actually received cytarabine, as compared with 95% in the first 3 months of the Italian study and 91% in the French study.

10.4. Crossover

Almost 40% of the patients who began on the Interferon/Cytarabine arm crossed over to the Gleevec arm, whereas only 1% of patients originally on the Gleevec arm crossed over to the Interferon/Cytarabine arm. The FDA expressed concerns regarding the effects of excessive crossovers on the study results, and the sponsor responded by requiring an independent Study Management Committee (SMC) to approve all requests for treatment crossover due to increasing WBC count or intolerance to treatment. Initially, crossover to the other treatment arm will occur under any of the following circumstances:

- Failure to demonstrate a complete hematologic response at 6 months
- Failure to achieve a major cytogenetic response at 24 months,
- Loss of complete hematologic response, provided that progression to accelerated or blastic phase did not occur,
- Intolerance of treatment,

After the primary endpoint was changed to time to progression, the crossover rules were also amended to the following:

- Loss of CHR
- Loss of MCR
- Failure to achieve a MCR or CHR at 12 months
- Increasing WBC count
- Intolerance of treatment

Reasons for crossover are summarized in the following table:

Table 20 Reasons for Crossover

Reason	Gleevec N=553 (%)	IFN+Cytarabine N=553 (%)
Number of patients who crossed over	7 (1.3)	218 (39.4)
Intolerance of treatment[1]	4 (0.7)	126 (22.8)
No CHR at 6 months[2]	0	41 (7.4)
No MCyR at 12 months[3]	0	1 (0.2)
No MCyR at 24 months	0	1 (0.2)
Progression :	3 (0.6)	49 (8.8)

1 Approved by SMC

2 Only before amendment 2 or in case the patient did not re-consent

3 Changed to '24 months' at amendment 3

The most common reason for a request for crossover from interferon to Gleevec was for intolerance to treatment. The SMC approved approximately two thirds or requests for crossover due to intolerance of treatment, and approximately three quarters of requests for crossover due to increasing white blood counts. A total of 218 patients crossed over from the interferon to the Gleevec arm, and 7 patients crossed over from the Gleevec to the interferon arm. An increase in the number of patients who dropped out of the interferon arm increased sharply with the marketing approval and subsequent introduction of Gleevec into the US market in May of 2001 which was not observed in countries where the product was not commercially available.

10.5. Patient Disposition

Table 19 displays the study patient disposition at the data cut off point as of January 31st, 2002.

Table 21: Patient Disposition

Disposition/Reason	First-line treatment		Second-line treatment	
	Gleevec	IFN+Ara-C	GLV >IFN	IFN >GLV
	N=553 (%)	N=553 (%)	N=7 (%)	N=218 (%)
Ongoing at time of cut-off	495 (89.5)	165 (29.8)	4 (57.1)	201 (92.2)
Crossed over to other treatment arm	7 (1.3)	218 (39.4)	0	0
Discontinued treatment	51 (9.2)	170 (30.7)	3 (42.9)	17 (7.8)
Adverse events	11 (2.0)	31 (5.6)	1 (14.3)	5 (2.3)
Unsatisfactory therapeutic effect	9 (1.6)	29 (5.2)	2 (28.6)	8 (3.7)
No longer required study drug (BMT)	5 (0.9)	7 (1.3)	0	2 (0.9)
Protocol violation	10 (1.8)	15 (2.7)	0	0
Subject withdrew consent	10 (1.8)	74 (13.4)	0	1 (0.5)
Lost to follow-up	2 (0.4)	6 (1.1)	0	0
Administrative problems	0	6 (1.1)	0	1 (0.5)
Death	4 (0.7)	2 (0.4)	0	0

While 553 patients were accrued to both arms, 218 patients crossed over from the interferon arm to the Gleevec arm and only 7 patients crossed over from the Gleevec to the interferon arm. Ninety percent of patients randomized to the Gleevec arm were still receiving

Gleevec at the time of data cut off, whereas only 30% of patients randomized to the interferon arm were still receiving interferon at the time of data cutoff. Thirty percent of patients randomized to interferon discontinued treatment, while less than ten percent of patients randomized to Gleevec discontinued treatment.

10.6. Conclusions

There were minor imbalances between treatment arms in terms of major protocol violations, dropouts, and previous treatment received. Patients on the Gleevec treatment arm receiving close to 100% of the planned dose intensity, and patients on the interferon arm receiving only 56% of the planned dose intensity. Twenty patients randomized to interferon withdrew consent prior to receiving the study drug, compared with only two patients on Gleevec. These imbalances all favored Gleevec treatment arm efficacy. Forty percent of patients on interferon were allowed to cross over to the Gleevec arm, compared with 1.3% of patients on Gleevec who crossed over to the interferon arm, further complicating the interpretation of the efficacy results.

11 EFFICACY RESULTS

11.1. Cytogenetic Responses

Cytogenetic analyses were to be performed every three months for the first 12 months of therapy and every six months thereafter, and on the last day of treatment. The primary analysis was to be on the intent-to-treat (ITT) population. Cytogenetic responses were protocol-defined in terms of the percentage of Ph chromosome-positive metaphases in bone marrow:

- complete cytogenetic response: 0% Ph-positive cells;
- partial > 0%-35% Ph-positive cells);
- minor > 35%-65% Ph-positive cells;
- minimal (> 65%-95% Ph-positive cells;
- None (> 95%-100% Ph-positive cells.

Complete and partial cytogenetic responses are referred to as major cytogenetic response, i.e. < 35% of Ph chromosome-positive metaphases in bone marrow. The minutes of the pre NDA meeting on 4/17/02 reflect an agreement that only confirmed cytogenetic responses should be counted. If an individual has a CCyR on one occasion and a PCyR on a different evaluation it will be scored as a PCyR, regardless of the order of the evaluations. If the order is reversed and no subsequent study is done it is still a PCyR. Confirmed MCyR rate should therefore be derived from those patients who had no worse than a PCyR on any of their aspirates, and confirmed C CyR should be from patients who had no worse than a CCyR on at least 2 visits. The sponsor either performed traditional or FISH analysis, either was acceptable.

11.1.1 Interim Analysis of Major Cytogenetic Response Rates at 1 year

Initially the interim analysis consisted of an analysis of the CHR rate and QoL endpoints at 6 months. Gleevec was to be considered active if the associated rate of CHR is non-inferior to the

rate on the control arm in conjunction with an improvement in QoL on the Gleevec arm over the QoL in the control arm. The interim analysis was amended to evaluate the major cytogenetic response (MCyR) rate at 12 months after all patients were enrolled, per amendment 2 of the protocol. Major cytogenetic response was defined as the sum of overall complete cytogenetic response (CCyR) and partial cytogenetic response (PCyR).

Table 22: Sponsor's Analysis MCyR Rates at 1 year

	Gleevec (n=553)	IFN+Ara-C (n=553)
Estimated McyR rate at 12 months	84.1%	29.8%
95% C.I.	81.05, 87.2%	24.9%, 34.6%
P value	< 0.001	
Estimated CCyR rate at 12 months	69.3%	11.5%
95% C.I.	65.3%, 73.2%	8.0%, 15.0%

On the basis of the interim analysis, the independent data monitoring committee examined preliminary results of other endpoints specified in the trial, and, on Dec 21, 2002, recommended that that the results of the interim analysis be made public and released to the investigators because of highly statistically significant differences in protocol specified events.

11.1.2 Overall cytogenetic response rates

Results of the sponsor's analysis of first line cytogenetic response rates are summarized below:

Table 23: Sponsor's First-line Cytogenetic Response Rates

	Gleevec (n=553)	Infra-C (n=553)
Best Rate of MCyR (%)	457 (82.6)	112 (20.2)
p-value*	<< 0.0000001	
Best Rate of CCyR (%)	375 (67.8)	41 (7.4)
95% C.I.	0.637-0.717	0.054-0.099
p-value*	<< 0.0000001	
Sponsor's Cytogenetic Response Rates Confirmed on ≥ 2 analyses		
Number of MCyR (%)	419 (75.8%)	67 (12.1%)
95% C.I.	0.720-0.793	0.095-0.151
p-value *	< 0.001	
Number of CCyR	297 (53.7%)	15 (2.7%)

* FDA statistical reviewer's results of Fisher's Exact Test

The FDA required that only cytogenetic responses confirmed on 2 evaluations would be accepted for registration. Confirmed cytogenetic results would report the lowest cytogenetic response following the initial response. If an individual had a CCyR on one occasion but a MCyR on a subsequent evaluation, the individual would be scored as a MCyR. The FDA results derived from a review of the primary data are summarized below:

Table 24: FDA confirmed Cytogenetic Response Rates (ITT principle)

	Gleevec	IFN+Cytarabine
ITT	**N = 553**	**N = 553**
Number (%) confirmed MCyR	326 (59.0%)	41 (7.4%)
95% C.I.	54.7%, 63.1%	5.4%, 9.9%
p-value*	1.24×10^{-80}	
Number (%) confirmed CCyR	146 (26.4%)	18 (3.3%)
95% C I.	22.8%, 30.3%	1.9%, 5.1%
p-value*	7.33×10^{-30}	

FDA statistical reviewer's results of Fisher's Exact Test

The denominator used for the ITT analysis was the total number of patients. Not all patients had bone marrow specimens that were adequate for analysis. The number of patients on each arm with >1 aspirates adequate for cytogenetic analysis was determined by the FDA reviewer to be 533 on the Gleevec arm and 490 on the interferon arm. The FDA medical reviewer recalculated the confirmed ITT cytogenetic response rates using the total number of ≥ 1 evaluable aspirates on each arm as the denominator. The FDA statistical reviewer preformed a statistical analysis on these response rates and the results are summarized below:

Table 25: FDA confirmed cytogenetic responses on patients with > 1 evaluable aspirates

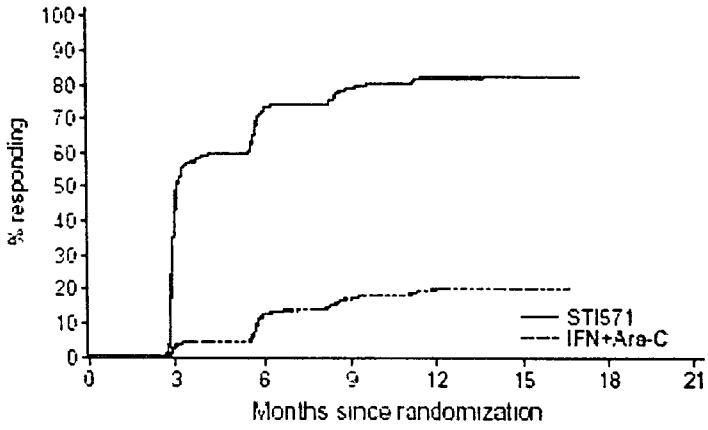
N (%) > 1 Evaluable Aspirates (ITT population)		
	Gleevec	**IFN+Cytarabine**
	N = 533	**N = 490**
Number (%) confirmed MCyR	326 (61.1%)	41 (8.4%)
95% C.I.	56.9%, 65.3%	6.1%, 11.2 %
p-value	8.05×10^{-76}	
Number (%) confirmed CCyR	146 (27.4%)	18 (3.7%)
95% C.I.	23.6%, 31.4%	2.2%, 5.7%
p-value	1.06×10^{-27}	

Reviewer comment: The FDA results showed lower confirmed cytogenetic response rates for the Gleevec arm and higher rates for the interferon arm, compared with the sponsor, however the FDA results for both major cytogenetic responses and complete cytogenetic responses in both the evaluable and the ITT populations are still highly statistically significant favoring the Gleevec arm. The reason for the difference between the FDA and sponsor analysis is not clear. The FDA and sponsor differed on the individual confirmed cytogenetic responses on over 100 individual patients. Reconciliation of these individual responses was thought to be impractical by the FDA reviewer and would not affect the overall conclusions of the study. Despite disagreements in the exact numbers, The FDA and sponsor are in agreement regarding the significant superiority of Gleevec treatment compared with interferon in terms of cytogenetic response rates.

11.1.3 Duration of Cytogenetic responses

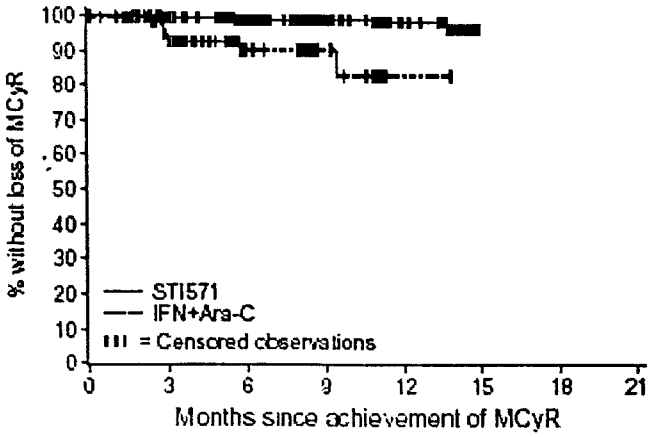
The sponsor performed an analysis of cumulative Major cytogenetic responses (first line) which showed that the median time to a MCyR was 3 months on Gleevec (range 2.2 to 17 months) and 8.4 months on interferon (range 2.8 to 16.4 months).

Figure 5: Cumulative Major Cytogenetic rates (first line)



The sponsor's analysis showed that sixteen patients lost their MCyR during first-line treatment (confirmed loss of MCyR or progression to AP or BC): 7 (1.5%) on Gleevec and 9 (8%) on IFN + Cytarabine. Of the 7 patients on Gleevec, 3 had lost a confirmed MCyR. Of the 9 patients on IFN – Cytarabine, two had achieved a confirmed cytogenetic response (PCyR) before loss of MCyR was documented. The sponsor's analysis of the duration of cytogenetic response is displayed below:

Figure 6: Sponsor's duration of MCyR



Responses appeared to be at least as durable on the Gleevec arm compared with the interferon arm. Valid comparisons cannot be made for loss of cytogenetic response, since the percentage that attained cytogenetic responses were unequal and those who lost cytogenetic response were not randomly divided between the two arms. However, the percentage of patients who lost their major cytogenetic response was higher in the interferon arm than on the Gleevec arm (Table 24)

Table 26: Sponsor's analysis of loss of major cytogenetic response

	Gleevec	IFN+Ara-C
No. of patients with MCyR	457	112
No. of patients who lost MCyR	7 (1.5%)	9 (8.0%)

11.1.4 Conclusions

In the FDA's analysis of evaluable patients with confirmed major cytogenetic responses, 61% of patients on Gleevec achieved a major cytogenetic response, compared with 8.4% 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, 27 % of patients on Gleevec achieved a confirmed complete cytogenetic response, compared with 3.7% on the interferon treatment arm. Although the actual results differed, 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). Eight percent of patients on interferon lost their major cytogenetic response compared with 1.5% on Gleevec. All analyses of cytogenetic responses favored the Gleevec treatment arm and were highly statistically significant.

11.2. Hematologic Responses

Complete hematologic response was a secondary endpoint of the trial, however, it was measured before progression, and the hematologic responses reflected the overall efficacy results. The following were required to be present for > 4 weeks for the attainment of a confirmed complete hematologic response:

- Normalization of peripheral blood counts, i.e. WBC < 10.0 x 10'/L and platelet count < 450 x 10 /L.
- Normal WBC differential (no peripheral blood blasts and promyelocytes, <5% sum of peripheral myelocytes + metamyelocytes)
- No evidence of disease-related symptoms and extramedullary disease, including spleen and liver
- No bone marrow or peripheral blood values indicating accelerated phase or blast crisis

11.2.1 Complete Hematologic Responses

Response rates on first line therapy are reported in Table 25 below:

Table 27: CHR rates (First-line treatment)

	Gleevec N=553	IFN+Cytarabine N=553
Sponsor CHR rate n (%) 95% CI	522 (94.4%) [92.1%, 96.2%]	302 (54.6%) [50.4%, 58.8%]
Fisher's Exact Test	p<0.001	
FDA CHR rate n (%)	518 (93.6%)	316 (57.1%)

The sponsor and FDA both reported a 94% complete hematologic response rate in the Gleevec first line treatment group. The sponsor reported a 55% and the FDA reported a 57% complete hematologic response rate in the control interferon treatment group prior to crossover.

Table 28: Complete Hematologic Response (ITT principle)

ITT principle	Gleevec N=553	IFN+Ara-C N=553
Sponsor's CHR rate n (%)	523 (94.6%)	423 (76.5%)
95% CI	[92.3%, 96.3%]	[72.7%, 80.0%]
Fisher's Exact Test	p<0.001	
FDA CHR rate n (%)	534 (96.6%)	451 (81.5%)

In the intent to treat analysis, patients that crossed over were analyzed on the basis of the treatment arm to which they were initially randomized. FDA and sponsor's analysis showed that the response rates were about 95% for patients randomized to receive Gleevec. Patients randomized to receive interferon had a 76% and 81% complete hematologic response rates by the sponsor's and FDA analysis, respectively. Analysis of response rates by second line treatment in the patients who crossed over demonstrated an 83.5% response rate for patients who were treated with Gleevec after crossing over from the interferon arm. Only seven patients crossed over from Gleevec to interferon, and these patients were reported to have a 43% response rate with wide confidence intervals due to the small numbers. Valid comparisons cannot be made for second line treatment, since patients who received second line treatment were not randomly divided. Overall second-line results showed that the response rates with Gleevec were substantially higher than with interferon and Cytarabine, and that treatment with Gleevec caused a complete hematologic responses in 83% of patients previously treated with interferon. Conversely, treatment with interferon caused a complete hematologic response in 43% of patients who crossed over from the Gleevec treatment arm (Table 26).

Table 29 Sponsor's analysis of second line CHR rates

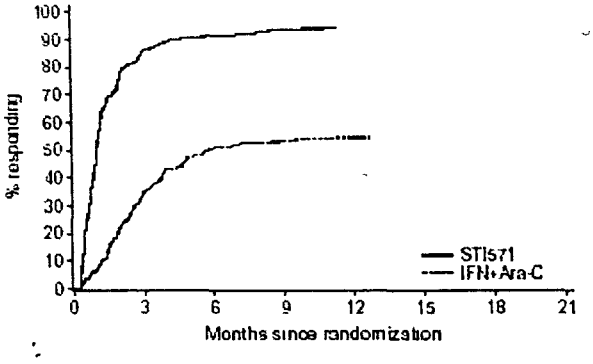
	Gleevec > IFN+Ara-C	IFN+Ara-C > Gleevec
Patients starting second-line treatment	N=7	N=218
CHR rate n (%)	3 (42.9%)	182 (83.5%)
95% CI	[9.9%, 81.6%]	[77.9%, 88.2%]

Complete hematologic responses were attained after crossover from either arm, however many more patients crossed over from interferon to Gleevec. The response rate observed in 218 patients who were treated with Gleevec after discontinuing interferon was 84%, compared with 43% in 7 patients who were treated with interferon after crossing over. In the analysis of CHR, patients who crossed over before responding are counted as 'non responders.' As many more patients randomized to IFN + Cytarabine crossed over in comparison to patients randomized to Gleevec, this approach could underestimate the rate of response to IFN + Cytarabine relative to Gleevec. Patients crossing over because of intolerance before having a chance to respond may bias the overall estimate when counted simply as 'non responders' as above.

11.2.2 Time to Complete Hematologic Responses

The estimated rate of CHR at 12 months using this approach is 95.9% for GLEEVEC and 66.6% for IFN + Cytarabine. This is similar to the published results of IFN +Cytarabine. The sponsor's data analysis suggest that CHR is achieved earlier with Gleevec in comparison to IFN and Cytarabine, with a median time to CHR of 1 month on Gleevec, versus 2.5 months on IFN. The sponsor's cumulative CHR rate is shown below in Figure 6:

Figure 7: Sponsor's Cumulative CHR rate, (first line treatment)



11.2.3 Duration of Complete Hematologic Response

The duration of complete hematologic response was well maintained for both arms with a greater duration for the Gleevec arm. The sponsor's plot of duration of CHR is displayed in the figure below: