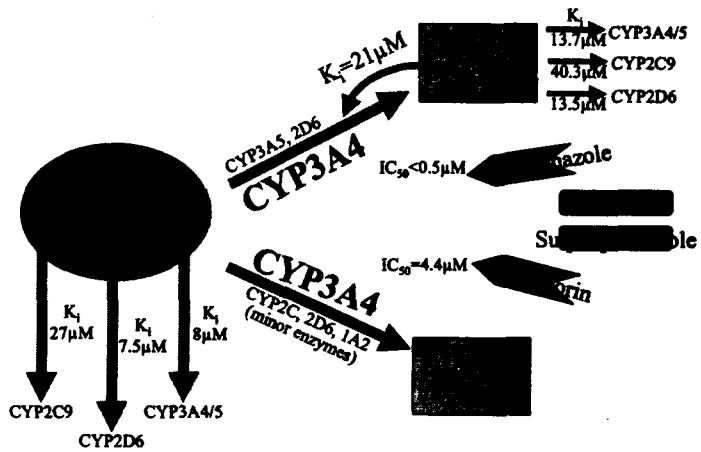
2. How is imatinib metabolized?

Based on the in vitro studies, the metabolism of STI571 is shown in the following figure.



N-desmethyl STI571 (CGP74588) is the major metabolite formed predominantly via CYP3A4. CYP3A5 and CYP2D6 may play a minor role in the formation of the metabolite. CYP3A4 is the major enzyme responsible for the biotransformation of STI571 in human liver microsome and in cDNA recombinant microsomes expressing specific CYP enzymes. CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 played a minor role in the biotransformation of STI571.

In pooled human live microsomes, 65% of the biotransformation was inhibited by ketoconazole at 1 to 2 μmole/L concentrations. Cyclosporin A also inhibited the formation of the metabolites with an IC_{50} value of 4.4 μmole/L at STI571 concentration of 25 μmole/L. Following is a table showing IC_{50} values of various drugs in human liver microsomes.

Drug Names	IC_{50} (μmole/L)
Ketoconazole	< 0.5
Cyclosporin A	4.4
Erythromycin	50
Doxorubicin	63
Paclitaxel	70
Ethynylestradiol	63
Terfenadine	54
Astemizole	86
Tamoxifen	200
Carbamazepine	> 200
Warfarin	> 200
Vincristine	> 200
Prednisone	> 200

Cimetidine	> 200

STI571 concentration: 25 μmole/L.

Quinidine and Sulphaphenazole, inhibitors of CYP2D6 and CYP2C9, respectively, at 4 μmole/L concentration didn't inhibit biotransformation of STI571.

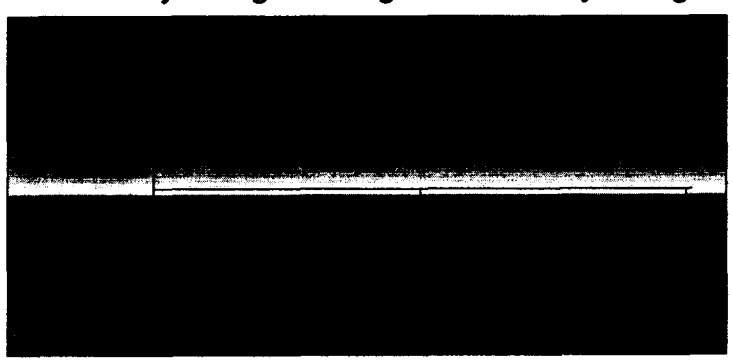
Human liver microsome studies demonstrated that STI571 was a potent competitive inhibitor of CYP2C9, CYP2D6 and CYP3A4/5 with K_I values of 27, 7.5, and 8 μmole/L, respectively. STI571 appears to be a competitive inhibitor of CYP1A2, CYP2A6, and CYP2C19 with estimated IC_{50} values of 410, 230, and 120 μmole/L, respectively. STI571 didn't inhibit CYP2B6, CYP2E1, and CYP4A9/11. In a pool of liver cytosol prepared from 10 individual donors, STI at 50 μmole/L concentration didn't inhibit metabolism of 5-FU (5 μM.) STI571 is possibly not an inhibitor of cytosolic dihydropyrimidine dehydrogenase, enzyme involved in the catabolism of 5-FU. In pooled human liver microsome, erythromycin and fluconazole inhibited the metabolism of STI571 with IC_{50} values of 50 and 118 μmole/L. Acetaminophen, acyclovir, allopurinol, amphotericin, cytarabine, hydroxyurea, norfloxacin, and penicillin V did not inhibit metabolism of STI571 in human liver microsome.

CGP74588 inhibited its own formation with a K_I value of 21 μM. The overall oxidative metabolism of STI571 was inhibited by CGP74588 with a K_I value of 59 μM. The K_M and V_{Max} values of CGP74588 formation from STI571 are 7.8 μM and 139 pmol CGP74588/min/mg. There is a low potential for inhibition of Paclitaxel metabolism by STI571.

In human liver microsome, CGP74588 inhibited CYP 3A4/5 (testosterone 6β-hydroxylation), CYP2C9 (S-warfarin 7-hydroxylation), and CYP2D6 (bufuralol 1'-hydroxylation) with K_I values of 13.7, 40.3, and 13.5 μM, respectively.

3. What is the role of metabolite?

The major metabolite of STI 571, N-demethylated piperazine derivative, CGP74588 showed similar *in vitro* potency as the parent. A comparison of its mean AUC vs. STI571 AUC following both once daily dosing of 25 mg and twice daily dosing of 1000 mg is



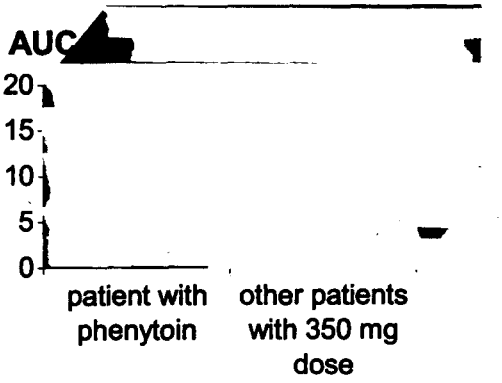
shown in the figure below.

The contribution of this major metabolite in the overall pharmacologic or toxic effect of Gleevec could not be assessed. Although the AUC of the major metabolite was 16% of the parent drug, low plasma protein binding of this metabolite could potentially play a role in the overall pharmacologic or toxic effect of Gleevec. Therefor, the applicant should assess the plasma protein binding of the N-demethylated piperazine derivative of STI571.

4. Is there any clinical relevance of the metabolism of the drug? Does metabolism of imatinib play a role in its overall activity?

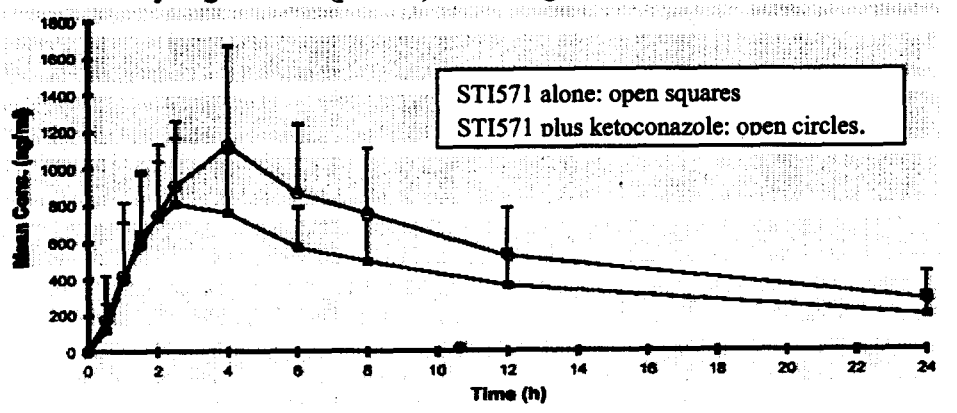
Yes. Metabolism (CYP3A4) plays a vital role in the overall safety and efficacy of the drug.

There are at least three evidences. A drug-interaction was observed involving the induction of metabolism of STI571. A patient treated at a dose of 350 mg daily with concomitant phenytoin therapy failed to respond hematologically and was found to have low plasma levels of STI571 as shown in the following figure.



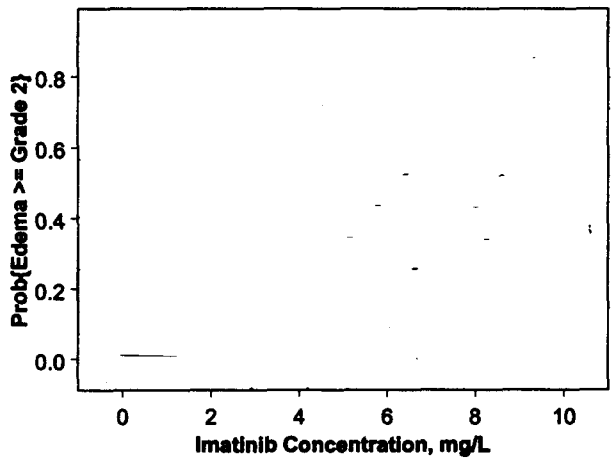
The patient promptly responded when phenytoin was stopped; though simultaneous dose escalation of STI571 to 500 mg was also performed. This is most likely due to the induction of CYP3A4 by phenytoin.

In a drug interaction study, following ketoconazole coadministration, the mean STI571 C_{max}, AUC_{0-24} and $AUC_{0-\infty}$ increased significantly by 26% ($p<0.005$), 40% ($p<0.0005$) and 40% ($p<0.0005$), respectively. Clearance of STI571 in presence of ketoconazole was reduced by 28.6% ($p<0.0005$). For the metabolite, the mean C_{max} and AUC_{0-24} of CGP74588 decreased significantly by 22.6% ($p<0.005$) and 13% ($p<0.05$) after ketoconazole treatment. However, the $AUC_{0-\infty}$ only decreased by 5% and this decrease was not statistically significant ($p=0.28$). The Figure below shows the mean plasma



concentrations of STI571 following oral administration of STI571 alone and when combined with ketoconazole. Since the study was conducted in normal volunteers, the clinical consequence of this interaction is unknown. However, STI571 dose should be reduced when coadministered with CYP3A4 inhibitors.

Using the concentration–edema model developed, the extent of interaction with ketoconazole can be quantitated. The probability of this adverse event is dependent on the age group. For younger blast crisis patients, co-administration of ketoconazole does not increase the probability of edema (Grade 2 or higher), however, for older patients the probability of having edema increases from 13 to 23%, for an average increase in



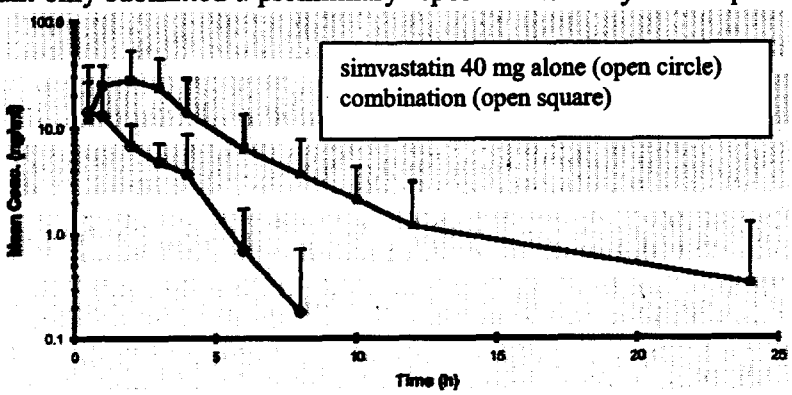
exposure by 40%.

Another drug interaction study in CML patients showed that coadministration of STI571 increased the C_{max} of simvastatin about 2-fold and $AUC_{0-\infty}$ about 3.5-fold compared to those of simvastatin alone. Also the half-life of simvastatin was prolonged from 1.4 to 3.2 h as shown in the following table.

	Simvastatin	Simvastatin plus STI571
t_{max} (h) *	1.6 (0.5 - 4.0)	1.7 (1.0 - 3.0)
C_{max} (ng/mL)	19.9 ± 21.0	37.9 ± 21.1
$t_{1/2}$ (h)	1.4 ± 0.9	3.2 ± 2.3
$AUC_{0\text{-}last}$ (ng•h/mL)	32.0 ± 25.4	121.9 ± 96.1
$AUC_{0\text{-}8}$ (ng•h/mL)	35.8 ± 26.3	133.1 ± 103.2
Vz/F (L)	2902 ± 2129	1657 ± 870
CL/F (L/h)	1567.3 ± 911.6	434.6 ± 216.5

The figure below shows the mean plasma concentrations of simvastatin after oral administration of simvastatin 40 mg alone and combined with STI571 400 mg once daily for 7 days.

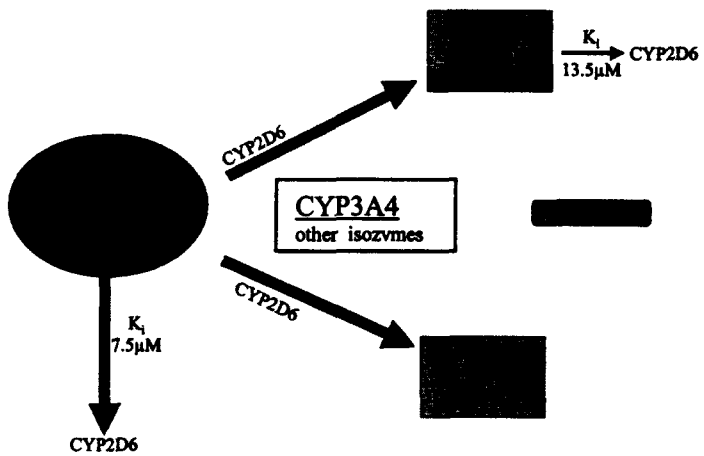
Since the applicant only submitted a preliminary report of the study with 9 patients (total



number of patients enrolled is 20), the clinical consequence of this study is unknown.
In summary, CYP3A4 mediated metabolism is involved in the total activity of imatinib. Drugs that are substrates, inhibitors, or inducers of CYP3A4 may have potential interactions with imatinib affecting either the safety or efficacy of the drug.

5. What is the role of CYP2D6?

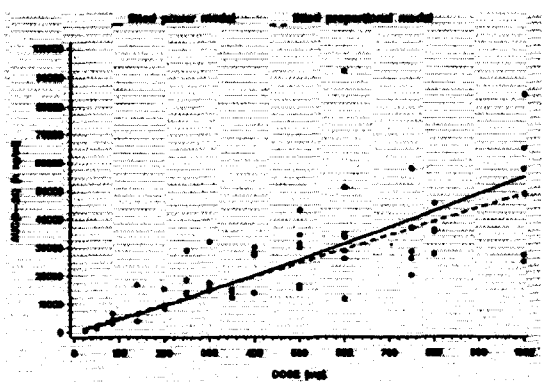
CYP2D6 played a minor role in the biotransformation of STI571 to form CGP74588, the major metabolite and other metabolites as shown in the following figure. Quinidine, a



potent inhibitor of CYP2D6, at 4 μM concentration did not affect the biotransformation of STI571, indicating an insignificant role of CYP2D6 in the metabolism of STI571. However, both STI571 and CGP74588 appear to be potent inhibitors of CYP2D6 with K_i values of 7.5 and 13.5 μM, respectively. The impact of CYP2D6 inhibition by STI 571 on the pharmacokinetics of drugs, which are substrates of CYP2D6, is unknown. Currently, no dosage recommendation can be made for patients who will be taking drugs that are substrates of CYP 2D6. Therefore, the applicant should assess potential drug interaction between imatinib and a substrate of CYP2D6.

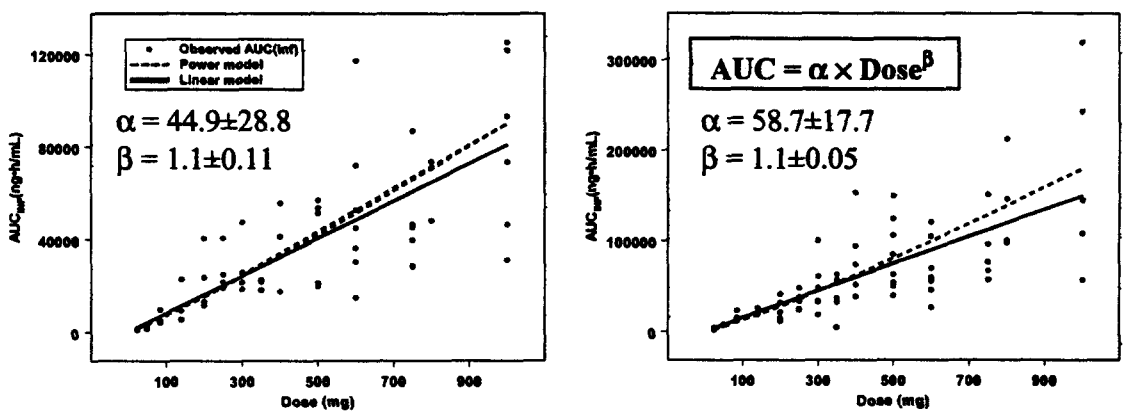
6. Is the dose proportionality established?

The recommended dose of Gleevec is from 400 mg to 800 mg daily depending upon the tolerability and the disease state. The applicant provided the following Figure to show the linear relationship between AUC_{0-24} and administered dose on day 1 after a single oral



dose of STI571. Similar relationship between the AUC_{0-24} and dose was obtained for the steady state.

In order to confirm if the relationship exists between the $AUC_{0-\infty}$ and dose, the reviewer checked the dose proportionality by fitting the $AUC_{0-\infty}$ data to a power model with proportion error. Similar results were obtained as shown in the following figure. The left panel shows the results on Day 1 and the right at steady state.



Therefore, the drug appears to be dose proportional in the dose range 25–1000 mg. However, the variability in AUC is high.

7. Is there any accumulation when multiple doses are given?

The following table is a comparison of PK parameters (mean ± SD) for STI571 on day 1 and at steady state.

Dose (mg)	$t_{1/2,day\ 1}$ (h)	$t_{1/2,ss}$ (h)	AUC_{ss}/AUC_{D1}*	$C_{max,ss}/C_{max,D1}$*
25	12.66 ± 1.79	14.50 ± 0.67	2.41 ± 0.73	2.43 ± 0.8
400	14.79 ± 5.79	19.31 ± 4.37	1.51 ± 0.57	1.14 ± 0.36
600	10.85 ± 2.03	15.60 ± 5.01	2.22 ± 2.79	1.72 ± 1.97
800	16.69 ± 3.72	19.63 ± 2.55	1.89 ± 0.76	1.68 ± 0.70
1000	11.13 ± 3.39	16.98 ± 5.44	1.76 ± 0.70	1.52 ± 0.98

*AUCss, Cmax,ss and AUC1,Cmax1 are values at steady state and on day 1, respectively. Both ratios can be used to estimate the accumulation index.

There is no significant accumulation of STI571 at steady state at doses between 25 and 1000 mg.

8. Is there any food effect on imatinib?

The food effect study was performed while patients were at steady state. As the tables show, when the drug was taken after consuming a fat-rich meal, t_{max} was later, AUC and C_{max} were lower and $t_{1/2}$ was longer than when the drug was taken in the fasting state for the parent drug. PK parameters for the N-methyl metabolite in the fed state showed a

similar pattern except for the fed state $t_{1/2}$ which was shorter than in the fasting state. Although the calculated 90% confidence limits for AUC_{0-24} of STI571, AUC_{0-24} of CGP74588 and AUC_{0-24} of CGP74588 lie outside the range of 80-125%, the applicant concluded that the differences in PK observed after food are not of potential clinical significance.

	Parameter	N	Ratio	90% Confidence-Interval
STI571	AUC_{0-24}	10	93.0	79.0-109.5
	C_{max}	10	88.7	76.8 – 102.4
CGP 74588	AUC_{0-24}	10	88.8	76.0-103.8
	C_{max}	10	84.2	70.7 – 100.3

It was difficult to observe changes in the pharmacokinetic behavior of STI571 once patients were at steady state. A better approach would have been to design a single dose crossover study in healthy volunteers with adequate washout periods. In the clinical trials, the patients were required to take Gleevec with food, and in the package insert similar recommendation is provided.

9. What is the permeability of STI571?

DPEI made a consult to DPQR pertaining to STI571 transport studies in Caco-2 cell monolayers. The conclusions are as follows.

- STI571 is a drug subject to efflux mechanisms and possibly active transporters.
- The Caco-2 studies were conducted at the concentration range of 1 to 50 μM. The Caco-2 permeability was found to be 0.95 x 10-6 cm/sec at 1uM and 7.9 x 10-6 cm/sec at 50 μM. The permeability values are consistent with the applicant's finding that STI571 is a substrate of an efflux pump where the permeability increases with increasing concentration. Based on the data and at the specific concentration range, the OTR/DPQR agreed with the applicant and concluded the STI571 was a low permeability compound.
- The dose strength of STI571 is 100 mg per capsule and the clinical dose is around 400 mg. According to the BCS guidance, this is equivalent to the concentration of 810 μM (dose strength) and 3239 μM (clinical dose) based on the molecular weight of 494 and BCS volume of 250 mL. At this high concentration, STI571 is expected to be a high permeability compound.

See APPENDIX III for detailed consult report.

10. Is there any formulation change during drug development?

The formulation changes made during the drug development are shown in the following table.

	5mg	25mg	50mg	50mg	50mg	50mg	100mg	100mg	100mg
	3752409	3752383	3752417	3752417	3752417	3752417	3752425	3752425	3752425

	00.001	00.001	00.001	00.002	00.003	00.004	00.001	00.002	00.003
STI 571									
Microcrystalline cellulose									
Crospovidone									
Silica, colloidal anhydrous/colloidal silicon dioxide									
Magnesium stearate									
Capsule contents									
Size 1, light yellow to orange yellow									
Size 1, orange to grayish orange, red inkbar									
Size 1, orange to grayish orange, red imprint NVR/SI									
Size 2, light yellow to orange yellow									
Size 3, light yellow to orange yellow									
Size 3, light yellow to orange yellow, red inkbar									
Size 3, light yellow to orange yellow, red imprint NVR/S									
Total capsule weight	130	215	240	163	163	163	304	306	306
* corresponds to 5, 25, 50 or 100mg base, respectively									

It is noted that the non-commercial formulations (3752383.00.001 and 3752417.00.001) for 25mg and 50mg strengths have been used in the clinical studies 03 001 (PK study), 0102 and 0109 (pivotal phase 2 studies). However, based on the drug supply, less than 5% of patients used these formulations in the pivotal trials 0102 and 0109. Therefore, the formulation change may not have significant impact in the overall safety and efficacy assessment of the drug in the pivotal trials.

11. Is the replacement of dissolution testing with disintegration time acceptable?

The applicant proposed to test the dissolution of the first ten STI571 50 mg and 100 mg capsule production size batches at release. If the batch data confirm the results obtained during development, the dissolution testing will be replaced by the determination of the disintegration time according to Ph. Eur./USP for release, with the following limit: "not longer than 10 minutes". The dissolution test will be maintained for stability testing of the drug product.

However, based on the ICH Guideline Q6A "Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances", replacement of dissolution testing by disintegration is allowed only when the criteria as set out in the decision tree #7 of this guideline (shown in the following chart) are met:

- Rapid dissolution (> 80% in 15 minutes) at pH 1.2, 4.0 and 6.8.

This criterion is fulfilled.

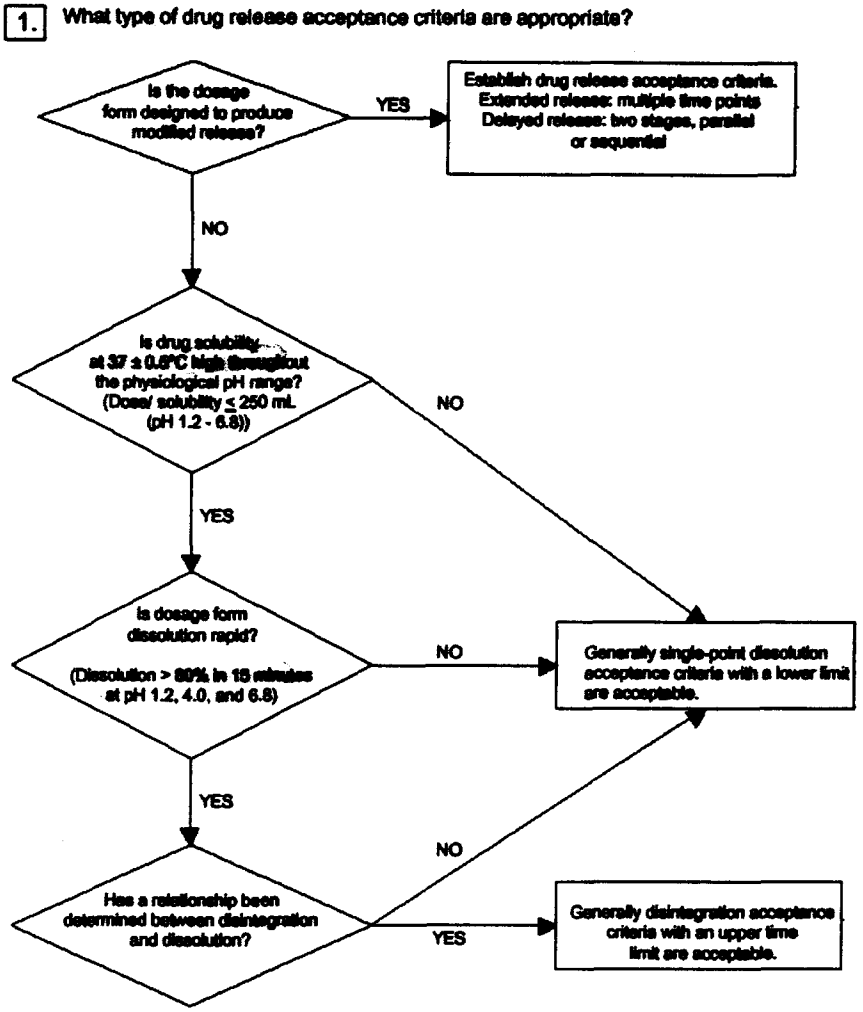
- High drug solubility at 37±0.5 °C throughout the physiological pH range (Dose/solubility ≤250ml at pH range 1.2-6.8).

STI571 mesylate is freely soluble up to pH 5.5, then, solubility reduces at higher pH values. The experiment was possibly conducted at room temperature.

- A relationship between disintegration and dissolution is determined.

A correlation between disintegration and dissolution data has not been determined.
Therefore, The replacement of dissolution testing by disintegration time is not acceptable.

Decision Tree #7



V. COMMENTS:

Phase 4 Commitment:

1. In vitro studies suggest that both STI571 and its major active metabolite are potent inhibitors of CYP2D6 isoenzyme. The impact of CYP2D6 inhibition by STI571 on the pharmacokinetics of drugs that are substrates of CYP2D6 is unknown. Currently, no dosage recommendation can be made for patients who will be taking drugs that are substrates of CYP2D6. Therefore, the applicant should assess potential drug interaction between imatinib and a substrate of CYP2D6. Please submit your study protocol for review.

2. Gleevec is predominantly metabolized by the liver and eliminated through the biliary route. Since there is no clinical study conducted with Gleevec in patients with liver impairment, no specific advice regarding dosing adjustment can be given to patients

with liver function insufficiency. Therefore, the applicant should conduct a pharmacokinetics study with Gleevec in subjects or patients with liver impairment. Please submit your study protocol for review.

3. The contribution of the major metabolite of STI 571, N-demethylated piperazine derivative, in the overall pharmacologic or toxic effect of Gleevec could not be assessed. Although the AUC of the major metabolite was 16% of the parent drug, low plasma protein binding of this metabolite could potentially play a role in the overall pharmacologic or toxic effect of Gleevec. Therefor, the applicant should assess the plasma protein binding of the N-demethylated piperazine derivative of STI571.

General:

1. The most important drawback of the submission is the lack of sound rationale for the dosing strategy. The available database does not permit derivation of an 'optimal' dose or concentration. The reviewer's analyses suggests the hypothesis that the 400 mg and 600 mg produce identical effects cannot be rejected. Further, the manifestation of edema appears to be concentration – dependent, particularly when the concentration is above ~ 4 mg/L. This aspect should be taken into account to optimize the dosing strategy of imatinib. Ongoing and future clinical trials should try to target particular concentrations below, equal to and above 4 mg/L and analyze the data to test if lower concentrations produce similar effectiveness as higher concentrations but with a better safety profile.

2. The population pharmacokinetic analysis is not acceptable. The comments regarding the analysis was sent to the applicant and included in the pharmacometrics review in Appendix IV.

3. The study regarding drug interaction with ara-C ([redacted] and pediatric study (P-103) were planned and are ongoing. Upon completion of the study, reports should be submitted to the Agency for review and proper labeling update.

4. A preliminary report of study [redacted] regarding the drug interaction between imatinib and simvastatin was provided in this NDA with data from nine patients. The final study report with all (twenty) patients should be submitted for Agency review.

4. The applicant performed the food effect study of Gleevec while patients were at steady state. It is difficult to assess true effect of food on the bioavailability and pharmacokinetics of a drug once patients are at steady state. A single dose crossover study in healthy volunteers with adequate washout periods would have been more appropriate to characterize the impact of food on the bioavailability of STI571. Since the patients are required to take Gleevec with food, no food effect study is recommended.

5. The dissolution specifications are set as follows.

Dissolution conditions:

Apparatus: Basket method (Apparatus 1)
Speed: 100 rpm
Test medium: 0.1 N hydrochloric acid
Volume: 1000 mL
Temperature: 37 ± 0.5 °C

Q value **not less than 80** % of the declared content dissolved in [redacted] minutes.

6. The applicant proposed to test the dissolution of the first ten STI571 50 mg and 100 mg capsule production size batches at release and if the batch data confirm the results obtained during development, the dissolution testing will be replaced by the determination of the disintegration time. This replacement of dissolution testing is not acceptable based on the following reasons.

- High drug solubility at 37±0.5 °C throughout the physiological pH range (Dose/solubility ≤250ml at pH range 1.2-6.8) has not been established.
  - A relationship between disintegration and dissolution has not been determined.

Labeling:

1. The following changes should be made in the **"CLINICAL PHARMACOLOGY"** section:

CLINICAL PHARMACOLOGY

Draft Labeling

2 pages redacted from this section of the approval package consisted of draft labeling

DRAFT

Draft

DRAFT

VI. RECOMMENDATION:

From the Clinical Pharmacology and Biopharmaceutics perspective, this NDA is acceptable. However, the applicant should commit to the phase 4 studies requested in this review.

Please forward the Phase 4 commitments, general, and the labeling comments to the applicant.

/S/

John Duan, Ph.D.
Reviewer

Date

Division of Pharmaceutical Evaluation I

/S/

Joga Gobburu, Ph.D. Date
Pharmacometrics Reviewer
Division of Pharmaceutical Evaluation I

/S/

Atiqur Rahman, Ph.D. Date
Team Leader
Division of Pharmaceutical Evaluation I

cc:	Orig 21,335	
	HFD-150	Division File
	HFD-150	AStaten, MCohen, JJohnson
	HFD-860	MMehta, ARahman, JDuan
	HFD-340	Vishwanathan
	CDR	

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pp. 137- 147

APPENDIX II. INDIVIDUAL STUDY SYNOPSIS

1. Dose finding Study 01 003.
Volume 1.37

Study title: A phase I, dose-finding study to determine the safety, tolerability, pharmacokinetic and pharmacodynamic profiles and to evaluate for preliminary anti-leukemic effects of STI571 in patients with chronic myeloid leukemia (CML) resistant to interferon-alpha (IFN).

Investigator & location: Brian J. Druker, MD; Charles L. Sawyers. MD; Moshe Tolpaz). Center 001: Oregon Health Sciences University, Portland, Oregon; Center 002: UCLA Medical Center, Los Angeles, California; Center 003: MD Anderson Cancer Center, Houston Texas.

Study period: June 22, 1998 to May 06, 2000

Study formulation: STI571 was supplied as 5, 25, 50, and 100 mg hard gelatin capsules for oral administration with following formulation control and batch numbers.

STI571	Formulation Control No.	Batch No.
5 mg	3752409.00.001	B970111
25 mg	3752383.00.001	B970083
50mg	3752417.00.001, 3752417.00.002, 3752417.00.003	B970084, X356 0999, X362 1199
100 mg	3752425.00.001,3752425.00.002	B970085, B990026, B990034, X365 1199, X024 0100

Objectives:
To evaluate the basic PK characteristics of STI571 and its metabolite (CGP 74588)
To assess the plasma concentrations and PK behavior after single and multiple doses
To examine the relationship between dose and drug exposure (AUC) and drug effect.

Subjects: Seventy patients participated in the study (64 adults and 6 children).

Study Design:
This is an open-label study carried out in 70 patients. Adult patients received 25, 50, 85, 140, 200, 250, 300, 350, 400, 500, 600, 750, 800 or 1000 mg daily, and patients <18

years received 175 mg/m^2 (doses of 125, 150. 200, 225. 425. and 425 mg daily). For the once daily dose regimen, blood samples were collected on Day 1 at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours after drug administration. At steady state blood samples were collected at 0.5, 1, 1.5, 2, 3, 4, 8, 24, 32 and 48 hours after drug administration. A 24 hour treatment-free period was maintained at steady-state after the 24 hour sampling for determination of terminal phase pharmacokinetic variables during the 32 and 48 hour steady-state measurements. For the b.i.d dose regimen (800 and 1000 mg total daily doses), blood samples were collected at 0, 1, 2, 3, 4, and 10 hours after the first dose (prior to the second dose), and 12, 13, 16, 24, 32, and 48 hours (after the second dose), both on day 1 and at steady-state. A 24 hour treatment-free period was maintained at steady state after the 24 hour sampling for determination of terminal phase pharmacokinetic variables during the 32 and 48 hour steady-state measurements. The non-compartmental PK parameters C_{max}, t_{max}, λ_Z, $t_{1/2}$, AUC_{0-24}, $AUC_{0-\infty}$, Vz/F, Cl/F, and accumulation ratio R_A were calculated from the plasma concentration-time profile. PK parameters at steady-state in relation to WBC reduction was analyzed.

Hematologic and bone marrow assessments were performed to detect anti-leukemic effects. WBC and platelet counts were used to determine complete hematologic response (CHR) in adults with chronic phase CML. Bone marrow examinations and cytogenic assessments were used to determine CHR and bone marrow response in patients with advanced Ph+ leukemias. Safety and tolerability were assessed by recording all adverse events reported or observed during the course of the treatment and by monitoring the results of standard clinical laboratory investigations, physical examinations, ECG and vital signs recordings throughout the study period.

Results:

Assay performance:

STI571 and CGP74588 were determined [redacted] The analyses were performed on [redacted]

Samples were prepared using [redacted] The validation results are shown in the following table.

Species	Range (ng/mL)	QC standard
STI571	8.53-10.7	95.8-99.0
CGP74588	7.6-12.8	95.5-101

The assays are acceptable based on the current standards. However, there were two methods ([redacted] methods) that have been used, but only one validation data set is presented in the report.

Pharmacokinetics:

STI571 was rapidly absorbed after oral administration with C_{max} being observed at about 2-4 hours post-dose. The C_{max} ranged from 72 ng/ml (at 25 mg) to 3395 ng/ml (at 600 mg) after once daily administration and from 2315 ng/ml (at 800 mg) to 3380 ng/ml (at 1000 mg) after twice daily administration as shown in the following tables and figures.

Table. PK parameters of STI571 in patients on Day 1 of administration

Dose/day mg (n)		t_{max} (h)	C_{max} (ng/ml)	λ_Z (/h)	$t_{1/2}$ (h)	AUC_{0-24} (μg•h/ml)	$AUC_{0-\infty}$ (μg•h/ml)	Vz/F (L)	CL/F (L/h)
25 (3)	Mean	2.2	71.6	0.056	12.7	0.7	1.0	461.6	24.8
	SD	0.8	17.9	0.008	1.8	0.2	0.2	172.0	6.0
50 (3)	Mean	1.8	185.6	0.090	10.1	1.4	1.91.9	377.2	28.3
	SD	1.0	56.6	0.065	5.1	0.3	0.50.5	145.9	7.7
85 (4)	Mean	2.0	444.7	0.064	11.7	4.3	5.8	261.7	16.3
	SD	1.4	209.2	0.023	3.6	1.6	2.6	82.7	5.2
140 (3)	Mean	1.8	889.3	0.053	13.3	8.9	12.3	306.8	16.1
	SD	1.0	757.7	0.006	1.5	6.9	9.1	183.0	10.3
200 (3)	Mean	4.0	846.0	0.045	18.9	11.0	21.5	273.3	12.7
	SD	3.6	197.1	0.022	11.6	3:7	16.3	66.3	6.7
250 (4)	Mean	2.6	1381.4	0.068	11.6	18.7	26.5	182.1	10.3
	SD	1.1	366.3	0.033	4.1	7.2	9.6	93.4	3.0
300 (5)	Mean	2.6	1640.0	0.052	13.8	19.0	27.4	237.2	12.1
	SD	2.1	443.0	0.009	2.3	7.3	11.5	68.0	3.7
350 (3)	Mean	2.5	1190.0	0.049	14.4	13.8	20.6	353.0	17.1
	SD	0.9	150.0	0.007	2.1	1.4	2.3	36.7	2.0
400 (4)	Mean	3.1	1907.5	0.051	14.8	24.8	38.8	236.0	12.5
	SD	2.0	355.0	0.016	5.8	7.4	15.9	76.5	7.2
500 (6)	Mean	3.8	2056.7	0.050	14.7	28.5	45.3	265.9	14.1
	SD	2.1	605.4	0.014	3.6	10.7	20.5	88.1	8.3
600 (7)	Mean	2.9	3395.0	0.066	10.9	39.7	52.4	245.5	16.6
	SD	1.4	2408.9	0.012	2.0	25.9	33.7	152.4	11.9
750 (6)	Mean	3.7	3016.5	0.072	10.6	34.4	45.6	279.6	18.9
	SD	2.3	1040.2	0.025	3.4	13.2	21.6	127.0	6.9

b.i.d regimen

800 (4)	Mean	14.0	2315.3	0.040	16.7	36.2	66.3	304.9	12.5
	SD	2.3	635.7	0.010	3.7	7.4	12.3	116.3	2.8
1000 (6)	Mean	12.2	3379.7	0.070	11.1	51.0	81.7	226.6	15.8
	SD	4.8	1547.4	0.030	3.4	22.7	38.7	106.3	9.5

Pediatric patients

125 (1)		3.0	2260.0	0.130	5.3	18.2	19.3	50.0	6.5
150 (1)		3.0	1640.0	0.060	11.0	19.9	25.9	92.1	5.8
200 (1)		2.0	3612.0	0.200	3.5	23.2	23.5	43.5	8.5
225 (1)		3.0	2586.0	0.050	14.7	36.7	56.8	84.2	4.0
425 (2)	Mean	3.5	3503.5	0.070	10.0	42.3	58.4	165.7	10.8
	SD	0.7	3413.2	0.010	1.5	47.1	47.1	149.7	8.7

Figure. Mean plasma concentrations on Day 1 after oral administration of STI571 at doses from 25 mg to 750 mg

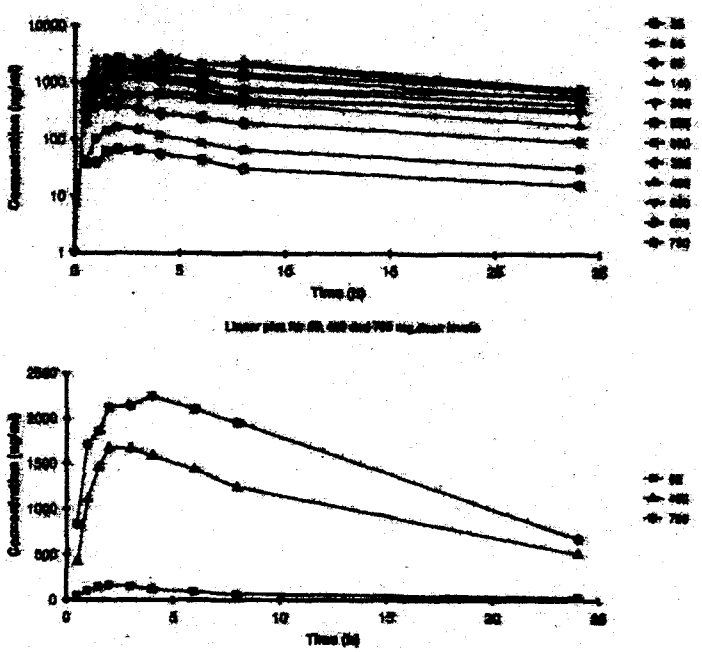


Table. PK parameters of STI571 in patients at steady state following once daily oral administration

Dose/day mg (n)		t_{max} (h)	C_{max} (ng/ml)	λ_z (/h)	$t_{1/2}$ (h)	AUC_{0-24} (µg•h/ml)	$AUC_{0-\infty}$ (µg•h/ml)	Vz/F (L)	CL/F (L/h)
25 (3)	Mean	1.0	179.9	0.050	14.5	1.9	2.7	345.3	16.5
	SD	0.5	89.2	0.000	0.7	0.9	1.4	214.5	10.0
50 (3)	Mean	3.8	365.7	0.050	15.1	4.6	7.0	239.6	10.9
	SD	3.6	75.6	0.010	3.3	0.4	0.5	70.7	1.0
85 (3)	Mean	2.2	799.6	0.040	19.4	9.8	16.1	254.2	9.3
	SD	1.4	463.1	0.010	4.1	3.3	5.6	70.9	3.1
140 (3)	Mean	1.7	1053.8	0.030	23.3	12.1	21.4	391.2	11.7
	SD	0.3	236.3	0.010	10.3	1.4	3.4	166.3	1.4
200 (4)	Mean	3.8	1026.7	0.050	14.7	12.9	19.2	393.7	18.2
	SD	2.9	572.9	0.000	1.6	6.1	8.9	187.1	7.8

Dose/day mg (n)		t_{max} (h)	C_{max} (ng/ml)	λ_z (/h)	$t_{1/2}$ (h)	AUC_{0-24} (µg•h/ml)	$AUC_{0-\infty}$ (µg•h/ml)	Vz/F (L)	CL/F (L/h)
250 (6)	Mean	2.1	1548.3	0.040	18.7	19.8	33.5	355.7	13.3
	SD	1.2	507.6	0.010	2.8	5.2	9.0	95.6	3.0
300 (6)	mean	6.4	1834.2	0.040	16.7	27.4	48.5	303.2	13,0
	SD	8.8	668.4	0.010	2.0	11.5	29.0	119.4	6.4
350 (5)	mean	3.1	1407.0	0,050	17.3	20.0	38.1	542.8	31.1
	SD	1.0	710.7	0.030	6.2	10.6	23.0	261.2	35.5
400 (5)	mean	3;3	2596.0	0.040	19.3	40.1	81.9	295.0	11.2
	SD	1.1	786.7	0.010	4.4	15.7	45.0	62.5	4.0
500 (9)	mean	4.0	2808.1	0.040	19.8	41.9	81.1	363.6	13.3
	SD	1.6	940.5	0.010	7.0	14.5	37.6	134.3	4.7
600 (9)	mean	3.1	3508.9	0.050	15.6	51.7	89.9	296.9	14.4
	SD	1.1	1649.3	0.010	5.0	26.7	74.2	102.5	6.8
750 (6)	mean	3.3	3804.8	0.050	15.0	56.4	85.4	324.6	14.7
	SD	1.0	1488.7	0.010	3.5	20.2	34.6	145.3	4.8
b.i.d regimen									
600 (4)	mean	2.3	2325.0	0,040	17.5	37.2	66.6	414.2	17.0
	SD	1.3	561.2	0.010	3.5	9.8	27.8	40.9	4.3
800 (4)	mean	7.8	3701.8	0.040	19.6	68.4	138.8	386.5	13;3
	SD	7.4	1433.5	0,000	2.6	29.8	53.8	179.2	5.0
1000 (5)	Mean	9.8	4478.0	0.050	17.0	82.5	174.1	386.02	16.44
	SD	9.8	2144.6	0,020	5.4	42.3	105.8	290.16	12.02
Pediatric patients									
125 (1)		3.00	2370.00	0.030	25.61	21.8	33.8	211.68	5.73
150 (1)		3.00	3840.00	0.080	9.17	49.3	59.9	40.31	3.05
200 (1)		2.00	4151.00	0.040	16.74	34.2	40.7	141.42	5.86
225 (1)		4.00	1600.00	0,040	16.00	20.7	31.3	250.77	10.87
425 (2)	mean	3.00	4654.50	0.04	17.44	64.1	106.3	196.63	7.63
	SD	0.00	2071.12	0.00	1.60	32.9	50.9	116.13	3.91

The following table provides a comparison of the main PK parameters for STI571 on Day 1 and at steady state. The comparison of AUC_{0-24} reveals a 1.5 - 3 fold drug accumulation after once daily dosing. In addition, the mean $t_{1/2}$ at steady state appears longer though this may have been due to the fact that the sampling schedule on Day 1 was too short to determine the true $t_{1/2}$. The last blood sample on Day 1 was taken only 24 hours after drug administration whereas at steady state the profiles included samples taken at 48 hours.

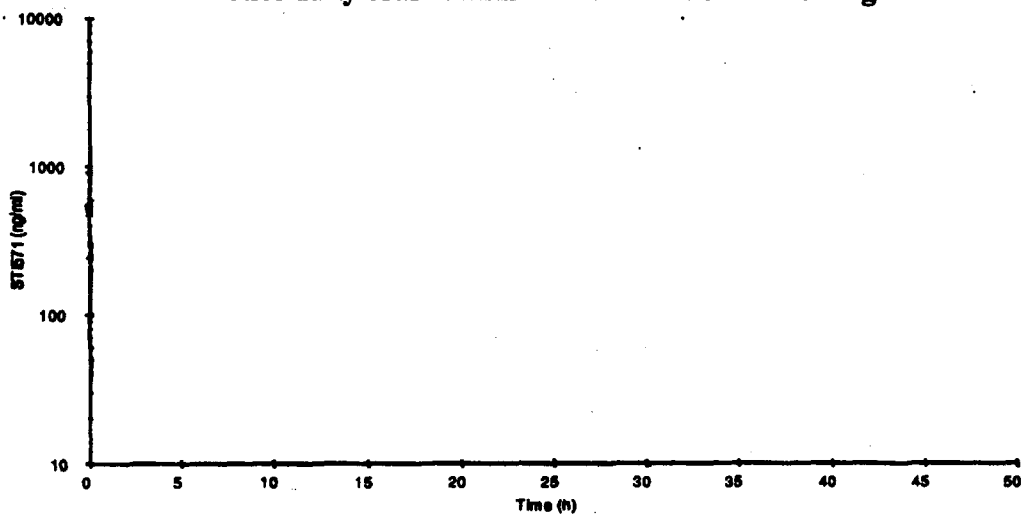
Table. Comparison of PK parameters on Day 1 and at steady state mean (SD)

Dose/day (mg)	$t_{1/2, day 1}$ (h)	$t_{1/2, SS}$ (h)	AUC_{SS}/AUC_{d1}	$C_{max, SS}/C_{max, d1}$
25	12.66 (1.79)	14.50 (0.67)	2.41 (0.73)	2.43 (0.80)
50	10.11 (5.12)	15.12 (3.29)	3.28 (0.64)	2.03 (0.35)
85	11.74 (3.63)	19.42 (4.13)	2.11 (0.09)	1.67 (0.25)
140	13.32 (1.51)	23.31 (10.31)	1.95 (1.30)	1.99 (1.76)
200	18.90 (11.56)	14.73 (1.56)	1.25 (0.86)	1.23 (0.68)

Dose/day (mg)	$t_{1/2,\ day\ 1}$ (h)	$t_{1/2,\ SS}$ (h)	AUC_{SS}/AUC_{d1}	$C_{max,\ SS}/C_{max,\ d1}$
250	11.59 (4.14)	18.66 (2.79)	1.26 (0.44)	1.26 (0.40)
300	13.78 (2.30)	16.69 (2.02)	1.69 (0.59)	1.26 (0.61)
350	14.39 (2.08)	17.25 (6.24)	1.75 (0.61)	1.42 (0.46)
400	14.79 (5.79)	19.31 (4.37)	1.51 (0.57)	1.14 (0.36)
500	14.69 (3.64)	19.81 (7.02)	1.46 (0.46)	1.29 (0.29)
600	10.85 (2.03)	15.60 (5.01)	2.22 (2,79)	1.72 (1.97)
750	10.63 (3.35)	15.02 (3.50)	1.70 (0.45)	1.29 (0.36)
800	16.69 (3.72)	19.63 (2.55)	1.89 (0.76)	1.68 (0.70)
1000	11.13 (3.39)	16.98 (5.44)	1.76 (0.70)	1.52 (0.98)

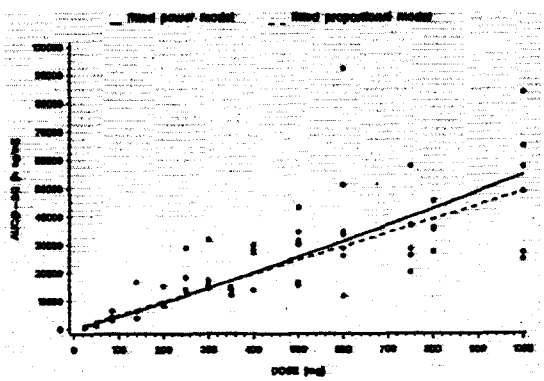
A comparison of the Day 1 and Day 28 PK profiles for STI571 in a representative patient treated at 400 mg daily (No 01/16) is given in the following Figure.

Figure. Plasma concentrations of STI571 in Patient 01/16 on Days I and 28 after once daily oral administration at a dose of 400 mg



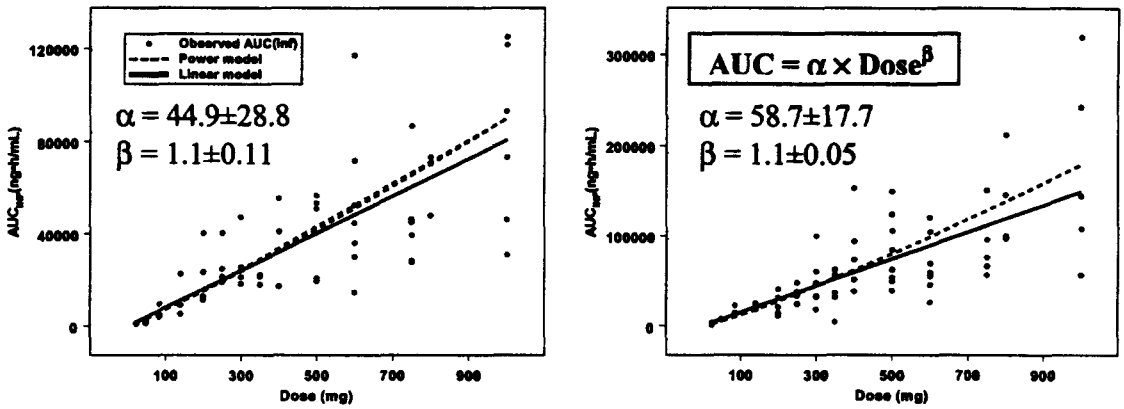
A drug-interaction was observed involving the induction of metabolism of STI571. A patient (01/14) treated at a dose of 350 mg daily failed to respond hematologically and was found to have inappropriately low plasma levels of STI571 ($AUC_{0\text{-}24}$ of 3.7 µg•h/ml in contrast to a mean $AUC_{0\text{–}24}$ of 20 µg•h/ml for other patients treated at 350 mg). The patient was receiving phenytoin, an anticonvulsant which is a potent inducer of liver P450 isoenzyme. The patient promptly responded when phenytoin was stopped, though simultaneous dose escalation of STI571 to 500 mg was also performed.

The relationship between dose and exposure was investigated on Day 1 and at steady state. As depicted in the following Figure, the increase in mean plasma AUC was

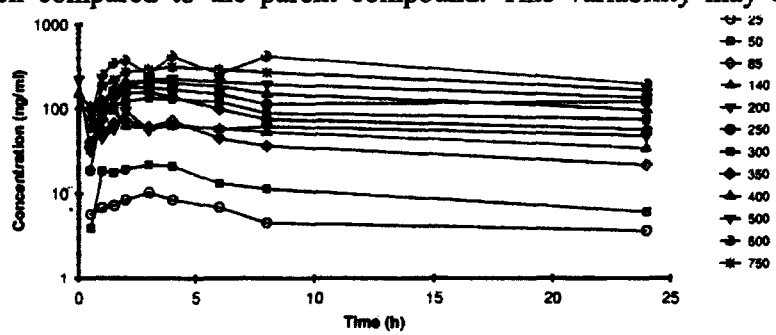


proportional to the administered dose. The analyses showed that the power model was adequate and 90% confidence intervals for the parameter were either close to 1 (at Day 1) or included 1 (at steady state). Therefore, dose-proportionality of the AUC was established for the dose range of 25 mg to 1000 mg, even though the 800 and 1000 mg daily doses were administered as divided doses.

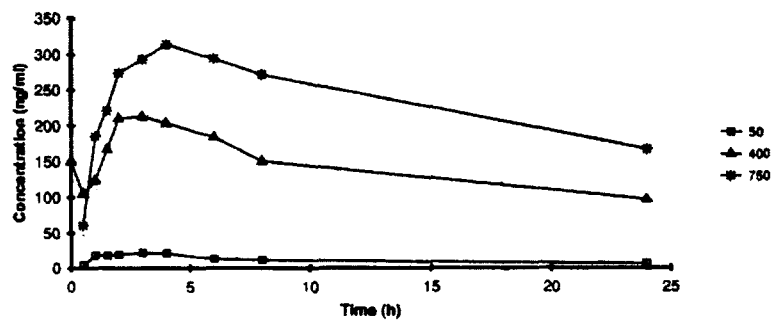
Since the applicant only examined the dose proportionality by using the AUC_{0-24} data on day 1 and at steady state, the reviewer verified the dose proportionality by fitting the $AUC_{0-\infty}$ data to a power model with a proportion error model. Similar results were obtained as shown in the following figure. The left panel shows the results on Day 1 and the right at steady state.



The main metabolite of STI571 in human liver S12 fractions *in vitro* was CGP 74588, the desmethyl derivative of the parent compound. CGP 74588 is also pharmacologically active. The terminal elimination of the metabolite was longer ($t_{1/2}$ 27-58 hours at steady state). There was also greater inter- and intra-patient variability in the PK parameters of CGP 74588 when compared to the parent compound. This variability may be due to



Linear plot for 50, 400 and 750 mg dose levels

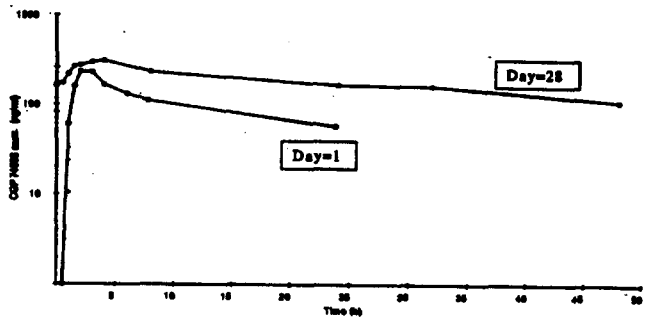


quantitative variations in CYP3A4 levels, the major cytochrome P450 isoenzyme involved in the microsomal biotransformation of STI571. In most patients, CGP 74588 could be detected in plasma 30 minutes (first sampling time) after oral administration of parent compound. The PK parameters of CGP74588 derived from the plasma concentration time curves on Day 1 (the Figures) are shown in the table below.

Table. PK parameters of CGP 74588 in patients on Day 1 of administration of STI571

Dose/day mg (n)		t_{max} (h)	C_{max} (ng/ml)	λ_Z (/h)	$t_{1/2}$ (h)	AUC_{0-24} (µg•h/ml)	$AUC_{0-\infty}$ (µg•h/ml)
25 (3)	mean	4.0	10.8	0.094	15.2	0.1	0.2
	SD	1.7	5.5	0.104	10.8	0.1	0.1
50 (3)	mean	2.7	25.3	0.077	16.4	0.2	0.4
	SD	0.6	12.7	0.081	10.7	0.1	0.1
85 (4)	mean	3.0	85.7	0.058	14.4	0.8	1.2
	SD	1.2	53.1	0.034	5.4	0.5	0.7
140 (3)	Mean	3.5	75.3	0.030	26.1	1.1	2.5
	SD	3.9	46.7	0.013	12,0	0.7	1.4
200 (3)	Mean	4.0	113.5	0.040	21.5	1.3	2.6
	SD	3.5	77.6	0.026	10.1	0.1	0.3
250 (4)	Mean	3.0	204,6	0.055	16.8	3.2	5.3
	SD	0.8	113.4	0.040	7.9	2.0	2.4
300 (5)	Mean	3.2	151.4	0.028	25.5	2.3	5.2
	SD	1.9	32.3	0.005	4.5	0.7	2.1
350 (5)	Mean	2.7	163.7	0.034	23.2	1.9	4.0
	SD	1.2	43.1	0.014	10.9	0.4	1.8
400 (4)	Mean	2.4	235.5	0.044	17.8	3.2	5.6
	SD	1.1	16.2	0.021	6.5	0.6	2.3
500 (6)	Mean	4.4	258.5	0.030	29.1	4.1	10.6
	SD	2.3	77.7	0.016	13.8	1.6	6.2
600 (7)	Mean	4.1	469.7	0.038	20.0	7.0	12.7
	SD	1.9	409.5	0.010	7.2	6.4	11.0
750 (6)	Mean	4.0	437.7	0.042	19.7	5.6	10.6
	SD	2.1	179.7	0.021	7.6	2.8	6.8
b.i.d regimen							
800 (4)	mean	8.5	230.1	0.020	32.5	4.1	12.6
	SD	6.6	33.1	0.010	9.4	0.5	2.8
1000(6)	mean	17.7	450.9	0.030	21.3	7.6	16.5
	SD	5.1	237.2	0.010	7.3	4.2	8.0
Pediatric patient[s]							
125 (1)		4.0	224.0	0.070	9.3	2.6	3.3
150 (1)		6.0	127.0	0.020	28.7	2.3	5.5
200 (1)		2.0	813.5	0.120'	5.6	7.2	7.6
225 (1)		4.0	243,0	0.030	23.1	4.1	8.5
425 (2)	Mean	5.5	516.6	0.030	20.1	8.4	18.6
	SD	3.5	514.2	0.000	1.7	9.9	18.3

A comparison of the Day 1 and Day 28 PK profiles for CGP 74588 in a representative patient (No 01/16) treated with 400 mg daily of STI571 is given in the following Figure.



After repeated administration, there was a 4-7-fold accumulation of metabolite at steady state following once daily dosing which was greater than that of parent drug. The increase in mean AUC and C_{max} in plasma was over-proportional to the administered dose, with some inter-patient variability.

The mean CGP74588/STI571 AUC ratio following both once daily dosing of 25 mg and twice daily dosing of 1000 mg was 0.14, indicating a limited contribution of metabolite exposure to total drug activity.

Conclusions:

1. The distribution and elimination of STI571 was multi-phasic with an apparent terminal half-life ($t_{1/2}$) averaging 10-23 hours.
2. Exposure (AUC) for parent drug was dose-proportional for the dose range of 25-1000 mg.
3. The main metabolite of STI571 was CGP 74588, the desmethyl derivative of the parent compound. CGP 74588 is pharmacologically active. The terminal elimination of the metabolite was longer ($t_{1/2}$ 27-58 hours at steady state). There was also greater inter- and intra-patient variability in the PK parameters of CGP 74588 when compared to the parent compound.
4. The comparison of AUC_{0-24} of parent drug at steady-state and on Day 1 revealed a 1.5-3 fold drug accumulation after repeated once daily dosing. For the major metabolite CGP74588, there was a 4-7-fold accumulation at steady state following once daily dosing.

Comments:

1. There were two assay methods that have been used. However, only one validation data set is presented in the report.
2. There was considerable inter-patient variability of absorption. The reason was postulated to be due, in part, to variation in protein binding between patients. However, variation in protein binding between patients is not adequately addressed in the submission.
3. Drug interaction was evidenced by decreased efficacy with coadministration of phenytoin. Effect of cytochrome P450 enzyme induction on the pharmacokinetics of Gleevec should be studied.

Study title: A study to assess the absorption, disposition, kinetics and biotransformation of radiolabelled drug and metabolites after a single oral dose of 200 mg [^{14}C]STI571 to healthy volunteers.

Investigator & location: ——

——

Study period: Nov. 04, 1999 to Nov. 10, 1999

Study formulation: [^{14}C]STI571 (methanesulfonic acid salt) from DMPK(CH), Isotope Laboratory, Novartis Pharma AG, Basel. Radiolabelled batch No. 7524509 (synthesis batch no. RSE052-2). Radiolabel in 2-position of pyrimidine ring. Specific radioactivity: 4.991 kBq/mg (0.135 µCi/mg). Radiochemical purity: 100%. Single doses of [^{14}C]STI571 (salt) were weighed into hard gelatin capsules (batch no. X3280999, by Isotope Laboratory and PHAD Basel).

Objectives:

To determine the rate and routes of excretion and the mass balance in urine and feces;
To determine the kinetics of STI571, total radioactivity and metabolites in blood/plasma
To identify and quantify the metabolites in plasma, urine and feces
To investigate the biotransformation pathways
To evaluate the absorption, if feasible
To determine the essential clearance mechanisms of STI571, if feasible

Subjects: Four healthy Caucasian male subjects, age 40-60 years, body weight within +15% of ideal body weight, screening passed within 3 weeks prior to first dose. Subjects were genotyped for CYP2D6 activity and none were poor metabolizers.

Study Design:

Four subjects received a single oral dose of 200 mg [^{14}C]STI571 (base =239 mg methanesulfonic acid salt; 1.18 MBq ^{14}C (=32 µCi)) in hard gelatin capsule. The nominal observation period after the single dose was 7 days. Blood, urine and feces were collected. Feces collection was continued in three subjects until day 12.

For plasma concentrations of STI571, CGP74588 and total ^{14}C-radioactivity, the parameters AUC_{0-t}, AUC_{inf}, C_{max}, t_{max}, $t_{1/2}$., Vz/f and CL/f were determined. From urine and feces concentrations of ^{14}C-radioactivity, the cumulative excretion (dose proportions)

per sample and the total excretion (mass balance) were determined. AUC of metabolites in plasma and balance of metabolites in excreta were determined. The chemical structures of main metabolites were identified by

The analytical methods used were as follows.

1.
2.

3.

4.

Results:

Assay performance:

STI571 and CGP74588 were determined in plasma by LC/MS/MS. The analyses were performed on . LC was carried out on a in column. Samples were prepared using solid phase extraction.

Species	Range (ng/mL)	Calibration Standard		QC standard	
		Precision (%)	Accuracy (%)	Precision (%)	Accuracy (%)
STI571					
CGP74588					

The performance of radioactivity assay is summarized in the following table.

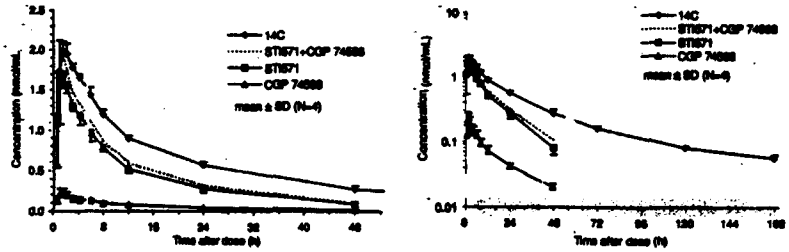
Matrix	Levels (dpm)	Mean (±SD) of the QC samples (%)
Whole blood	158, 519, 985	93.7 ± 4.5
Plasma	108, 537, 1086	99.0 ± 5.0
Urine	198, 820, 4261	100.8 ± 4.1
Feces	381, 1810, 8372	100.8 ± 2.2

The assays are acceptable based on the current standards.

Metabolism & Pharmacokinetics:

Several mechanisms appear to contribute to the clearance of STI571, including transport as well as various metabolic pathways.

The plasma concentration profiles of various species are shown in the following figures.



The pharmacokinetic parameters are summarized in the following table.

Key Pharmacokinetic Parameters:

(Parameters for Plasma Concentrations)	AUC_{0-48h} (mean ± SD) [nmol·h/mL] [a,b]	AUC_{0-48h} (mean ± SD) [% of total ^{14}C] [a,b]	AUC (mean ± SD) [nmol·h/mL]	C_{max} (mean ± SD) [nmol/mL] [a]	Terminal $t_{1/2}$ (mean ± SD) [c] [h]
^{14}C (total drug, i.e. including metabolites)	34.6 ± 1.7	100%	53.1 ± 2.0	2.02 ± 0.09	57.3 ± 12.5 (72-168 h)
STI571	20.0 ± 1.8	58% ± 3%	21.6 ± 2.3	1.87 ± 0.19	13.5 ± 0.9 (12-48 h)
CGP 74588 N-desmethyl metabolite	2.85 ± 0.37	8% ± 1%	3.47 ± 0.39	0.24 ± 0.05	20.6 ± 1.7 (12-48 h)
Total of 2 compounds	22.9 ± 1.9	66% ± 3%	25.1 ± 2.3	–	–

Following administration of oral dose of 200 mg, [^{14}C]STI571, C_{max} of STI571 and the total radioactivity was reached 1 to 2 hours after dosing. No or minimal first-pass metabolism appears to occur. Two thirds of ^{14}C-AUC_{0-48h} were covered by unchanged drug and the main metabolite CGP 74588. About one third of ^{14}C-AUC was accounted for by minor unidentified metabolites. The extent of absorption was estimated to be approximately 70% of dose, based on the amount of dose excreted in urine, and the amount of dose excreted between 72 and 264 h in feces, and the amount remaining in the body at study termination.

The ^{14}C-radioactivity was excreted slowly, mainly in feces. STI571 showed a low clearance, with a mean plasma half-life of 13.5 hours. Total radioactivity (sum of STI571 and metabolites) was eliminated in a multi-exponential manner with a terminal half-life longer than two days. Excretion of radioactivity was largely with the feces (mean: 68% of dose). Renal excretion was minor (13%). The bulk of the dose was recovered within 7 days (80%). Small proportions of the dose were recovered between day 8 and day 11. After 11 days, excretion was not complete and still continued with approx. 0.6% per day.

The metabolite patterns in plasma at 2 and 8 hours after dosing showed STI571 (P1) as the main component, followed by N-desmethyl metabolite (CGP 74588). Additionally, several minor peaks might be present. The major component in feces was STI571 (20% of dose) and CGP 74588 (9%). CGP 71422 was of minor importance (3%). Other minor metabolites were detected but not identified. Fecal excretion may have been due partly to unabsorbed drug. In urine, the main radioactive compounds were STI571 (5%) and CGP 74588 (1.5%). The sum of the metabolites CGP 74588 and CGP 71422, and of other minor unidentified metabolites accounted for at least 35% of the dose in the excreta. Thus

oxidative metabolism, catalyzed mainly by CYP3A, may be a major elimination mechanism.

Balance of metabolites in the excreta is shown in the following table.

Compound	Peak	Feces (0-168 h)	Urine (0-72 h)	Total of Feces and Urine
		% of dose (mean ± SD, N = 4)		
CGP 71422 (piperazine-4-N-oxide)	P3*	3.4 ± 0.8	0.5 ± 0.1	3.9 ± 0.9
CGP 74588 (N-desmethyl)	P2*	9.2 ± 1.8	1.5 ± 0.4	11 ± 2
STI571	P1	20 ± 4	5.4 ± 1.7	25 ± 5
undefined peaks		15 ± 4	4.4 ± 0.9	20 ± 4
Total of Peaks/recovered ^{14}C		48 ± 8	12 ± 2	59 ± 9
Not recovered from .		7.0 ± 2.3	0	7.0 ± 2.3
Not recovered from sample processing		12 ± 6	0	12 ± 6
Total analyzed in pool		66.9 ± 4.5	11.8 ± 1.5	78.8 ± 5.2
Total excreted in indicated period		66.9 ± 4.5	11.8 ± 1.5	78.8 + 5.2
Total excreted in period 0-264 h (N=3)		67.9 ± 4.4	13.2 ± 1.6	81.1 ± 4.9

*contains an additional metabolite of STI571 of molecular mass: 509 (=M+oxygen) as shown by LC-MS.

In both feces and urine, STI571 was the main component (P1). CGP 74588 (P2, the main metabolite) and CGP 71422 (P3) were identified by LC-MS. In urine as well as in feces extract, several metabolites of STI571 with the same molecular mass of 509 (M+oxygen) were detected by LC-MS. They contributed less than 4% and 0.5% of the dose each in feces extract and urine, respectively.

CGP 53715, a potential degradation product (aromatic amine moiety of STI571) was neither detected in feces extract nor in urine by [illegible] and LC-MS. STI571 appeared to be stable regarding benzamide-bond hydrolysis in the gastrointestinal tract.

Conclusions:

1. This study showed the rates and routes of excretion and the mass balance in urine and feces.

2. Following administration of oral dose of 200 mg, [^{14}C]STI571 was absorbed with C_{max} of STI571 and the total radioactivity reached 1 to 2 hours after dosing.

3. In both feces and urine, STI571 was the main component. CGP 74588 was the main metabolite.

4. The ^{14}C-radioactivity was eliminated slowly, mainly in feces, in a multi-exponential

manner with a terminal half-life longer than two days. STI571 showed a low clearance, with a mean plasma half-life of 13.5 hours. The excretion was not complete after 11 days.

5. Unchanged drug and the main metabolite CGP 74588 covered two thirds of ^{14}C-$AUC_{0\text{-}48h}$. About one third of ^{14}C-AUC was accounted for by minor unidentified metabolites.

6. Oxidative metabolism, catalyzed mainly by CYP3A, may be a major elimination mechanism.

3. Absolute Bioavailability Study 0108.
Volume 1.40

Study title:

A single-center, open-label, three-period, three-treatment, randomized, crossover study to investigate the absolute bioavailability of a single oral dose of STI571 400 mg in form of a hard gelatin capsule and STI571 400 mg oral solution compared with STI571 up to 100 mg given as an intravenous injection.

Investigator & location: ——

Study period: Jul 20, 2000 to Oct 28, 2000

Study formulation: STI571 was provided as 100 mg hard gelatin capsules (Formulation No. KN 3752425.00.002, Batch No. X0210100), as powder for solution (250 mg/vial) for oral use and i.v. infusion (Formulation No. KN 3758877.00.001, Batch No. Y03110200).

Objectives:
Primary objective was to investigate the absolute bioavailability of a single oral dose of STI571 400 mg in form of a hard gelatin capsule and STI571 400 mg oral solution compared with STI571 100 mg given as an intravenous injection. Secondary objective was to investigate the tolerability of intravenous doses of ST1571.

Subjects: Pilot Phase: 3 subjects, Main study Phase: 12 subjects (healthy, non-smoking, males and post-menopausal or sterile females aged 40- 60 years).

Study Design:

During the pilot phase, 3 healthy volunteers received a single, 60-min. i.v. infusion of 30 mg STI571. Based on the mean plasma concentration of the parent compound at the end of the infusion, the i.v. dose level for the main study was determined.

The main study was an open-label, three-treatment, three-period, randomized crossover study. Subjects received an oral dose of 400 mg STI571 in capsule form, 400 mg STI571 as an oral solution, and 100 mg STI571 i.v. infusion in random sequences with a minimum 7-day washout phase between treatments.

Physical examination, electrocardiogram (EGG), vital signs, laboratory safety evaluations (hematology, blood chemistry, urinalysis), special laboratory evaluation (genotyping of CYP2D6), monitoring of adverse events (AEs).

Sampling times for I.V. were 0.25, 0.5, 0.75, 1, 1.25, 1. 2, 2.5, 4, 6, 12, 36, and 72 hours post dose and for oral administration were 0.5, 1, 1.2, 2.5, 4, 8, 24, 48, and 96 hours post dose. The PK profile were obtained after single administration of 400 mg STI571 as a capsule, 400 mg STI571 as an oral solution, and 100 mg STI571 as an I.V. infusion to determine absolute bioavailability, and to provide a descriptive exploratory PK analysis.

Results:

Assay performance:

STI571 and CGP74588 were determined in plasma LC/MS/MS. The analyses were performed on [redacted] LC was carried out on [redacted] column. Samples were prepared using protein precipitation with acetonitrile.

STI571	[redacted]

The assay is acceptable based on the current standard.

Pharmacokinetics:

Following a 400 mg oral dose, STI571 was completely absorbed and was almost completely bioavailable (>97%). The oral solution was bioequivalent with the capsule formulation of STI571 as assessed by comparing AUC, C_{max} and t_{max} of the parent compound.

Figure. Mean plasma concentration - time profile of STI571 following i.v. (100 mg) and p.o. (400 mg) administration; capsule (open circles), solution (open squares), i.v. (open diamonds)

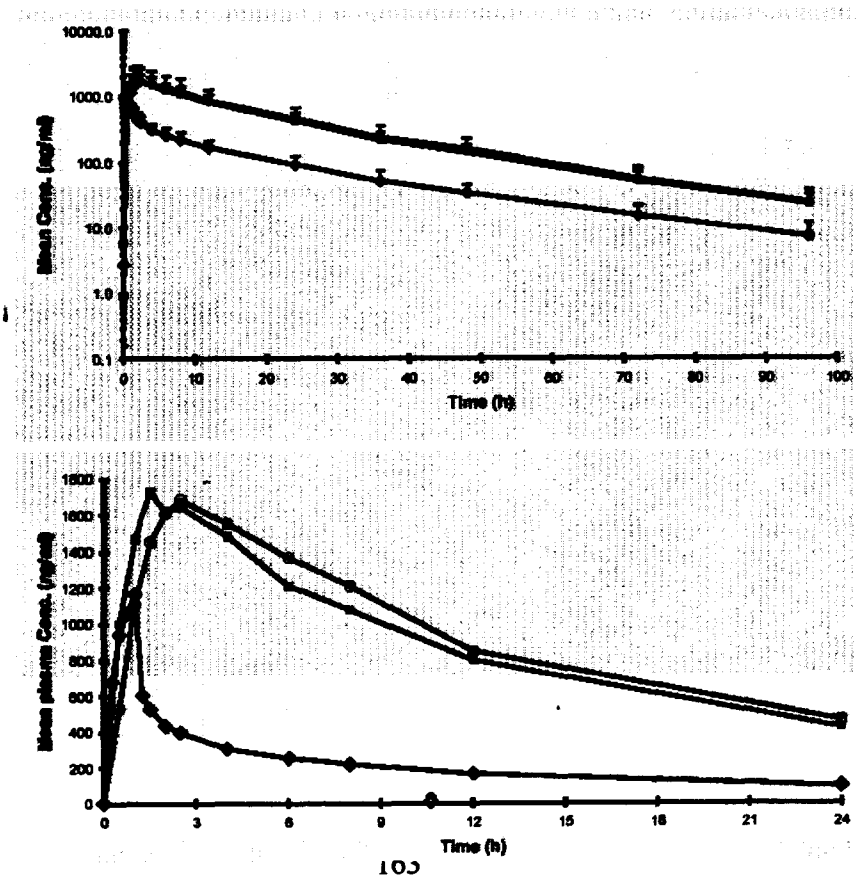


Table. Pharmacokinetic parameters – STI571 i.v. and p.o.

	Capsule (400 mg)	Solution (400 mg)	I.V. infusion (100 mg)
t_{max}(h)*	2.5 (1.0 - 6.0)	2.0 (1.5 - 4.0)	1.0 (0.5-1.0)
C_{max} (ng/mL)	1822 ± 1193	1848 ± 805	1206 ± 295
t ½ (h)	17.9 ± 3.1	18.3 ± 2.7	21.9 ± 4.3
AUC_{last} (ng•h/mL)	31976 ± 16329	30105 ± 9463	7556 ± 2136
$AUC_{0-\infty}$ (ng•h/mL)	32640 ± 16501	30729 ± 9573	7836 ± 2185

* median (range), others are mean±SD

Table. Absolute and relative bioavailability of STI571

	Capsule (400 mg)	Solution (400 mg)	I.V. infusion (100 mg)
$AUC_{0-\infty}$ (ng•h/mL) (arithmetic mean)	32640	30729	7836
$AUC_{0-\infty}$ (ng•h/mL) (geometric mean)	29607	29261	7527
F (absolute bioavailability) (90% CI)	98.3% (87.3%-111%)	97.2% (86.3%-110)	Reference
F (relative bioavailability) (90% CI)	101.3%* (90.8%-112.9%)*	reference	

* the reviewer's calculation

The ratio of C_{max} of STI571 between treatments of solution (400 mg) and capsule (400 mg) was 107.3% with 90% confidence interval of 96.7% to 119.1%.

No significant abnormalities in laboratory values, vitals signs or ECGs were reported in this study.

Conclusions:

1. This study showed that the bioavailability of STI571 tablets is greater than 97%.

2. Based on the data provided, the bioequivalence between the capsule formulation and oral solution has been established.

4. Drug Interaction Study 0119.
Volume 1.40

Study title: An open-label, randomized, crossover study to investigate the effects of ketoconazole (a potent inhibitor of CYP450 3A4) on the pharmacokinetics of STI571.

Investigator & Location:

Drug Formulation: STI571 100mg hard gelatin capsules (Batch No. X023 0100, Formulation No. KN 3759594.00.001). Ketoconazole 200 mg Tablets (Nizoral®)

Study period: Sep. 8, 2000 to Nov. 3, 2000

Objectives:
Primary objective is to investigate the effect of the coadministration of ketoconazole on the pharmacokinetics of STI571. Secondary objective is to investigate the tolerability of STI571 alone or in combination with ketoconazole.

Subjects: Fourteen healthy non-smoking subjects (13 males and 1 post-menopausal or sterile female) between 40 and 60 years of age were enrolled in this study.

Study Design:
This was a single center, open-label, randomized crossover design study. Each subject received an oral dose of 200 mg of STI571 in capsule form immediately after breakfast in the presence or absence of the oral coadministration of 400 mg ketoconazole in different sequences with a minimum 7-day washout period. Subjects were allocated at random to one of two treatment sequences.

For each subject went through a 21-day screening period, the two treatment periods each containing a baseline evaluation (12-14 hours prior to dosing), the drug administration and a 48-hour post-dose observation and PK sampling phase, and a study completion evaluation about 96 h after the last dosing. Blood samples for determination of STI571 plasma concentrations were taken up to 96 hours after dosing.

To investigate the effects of ketoconazole on the PK of STI571, the parameters: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, Vz/f and CL/f were determined for STI571 and the major metabolite CGP 74588. The data were analyzed by an analysis of variance and by confidence intervals for the ratio STI571+ketoconazole/STI571. A "no-effect" boundary was defined as (0.75, 1.50).

For evaluation of safety and tolerability, physical examination, electrocardiogram (ECG), vital signs, laboratory safety evaluations (hematology, blood chemistry, urinalysis), special laboratory evaluation (genotyping of CYP2D6), monitoring of adverse events (AEs) were performed.

Results:

Assay performance:
STI571 and CGP74588 were determined in plasma LC/MS/MS. The analyses were performed on [redacted] was carried out on [redacted] LC [redacted] column. Samples were prepared using protein precipitation with acetonitrile.

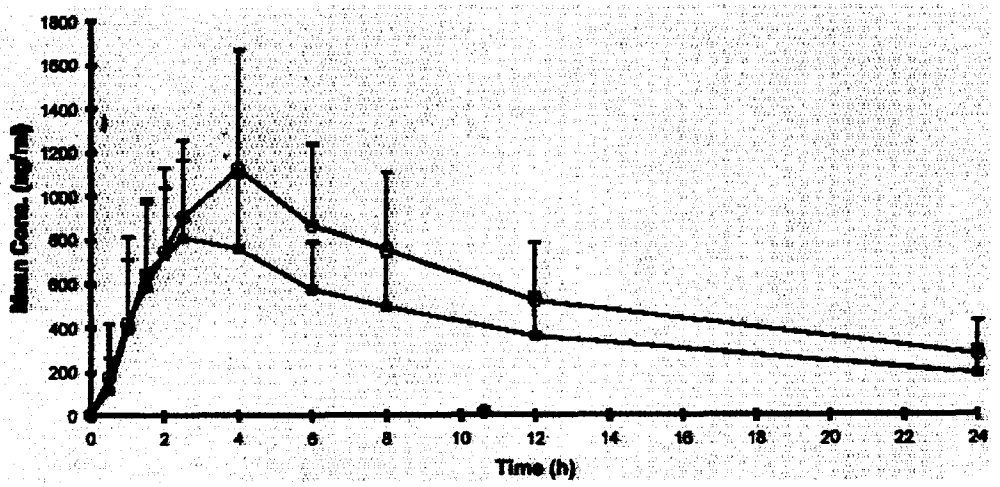
[redacted]

STI571 [redacted]

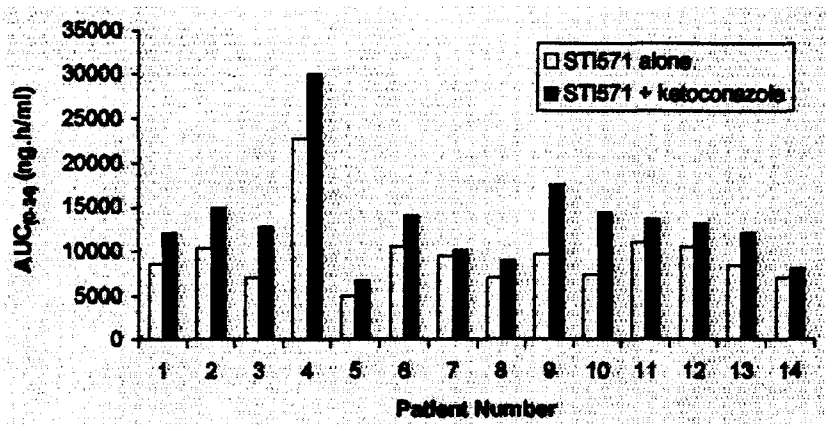
The assay is acceptable based on the current standard.

Pharmacokinetics:
Following ketoconazole coadministration, the mean STI571 C_{max}, AUC_{0-24} and $AUC_{0-\infty}$ increased significantly by 26% ($p<0.005$), 40% ($p<0.0005$) and 40% ($p<0.0005$), respectively. There was a statistically significant decrease in CL/F with a mean reduction of 28.6% ($p<0.0005$). For the metabolite, the mean C_{max} and AUC_{0-24} of CGP74588 decreased significantly by 22.6% ($p<0.005$) and 13% ($p<0.05$) after ketoconazole treatment. However, the $AUC_{0-\infty}$ only decreased by 5% and this decrease was not statistically significant ($p=0.28$). The Figure below shows the mean plasma concentrations of STI571 following oral administration of STI571 alone and combined with ketoconazole

STI571 alone: open squares, STI571 plus ketoconazole: open circles.



The following figure compares AUC_{0-24} of STI571 following oral administration of STI571 alone and combined with ketoconazole.



The following table presents STI571 PK parameters following oral administration of 200 mg STI571 alone and combined with oral administration of 400 mg ketoconazole

	STI571 plus ketoconazole	STI571 alone
t_{max} (h)*	4.0 (2.0 - 6.0)	2.5 (1.5 - 4.0)
C_{max} (ng/mL)	1213 ± 528	942 ± 311
$t_{1/2}$ (h)	19.2 ± 4.5	20.5 ± 4.4
AUC(0-24) (ng•h/mL)	13498 ± 5561	9618 ± 4191
AUC(0-∞) (ng•h/mL)	19667 ± 8932	14228 ± 7359
Vz/F (L)	318 ± 113	472 ± 163
CL/F (L/h)	11.6 ± 4.0	16.3 ± 5.5

all unflagged values are mean ± SD
* = median (range)

The ratios of AUC and C_{max} for 'STI571+ketoconazole'/'STI571' and corresponding 90%-confidence-Intervals (%) for STI571 and CGP74588 are shown in the following tables.

Species	Parameters	Ratio (combination/STI571 alone)	90% confidence interval
STI571	$AUC_{0-\infty}$	140.1	131.0-149.9
	C_{max}	125.7	112.3-140.7
CGP74588	$AUC_{0-\infty}$	95.0	87.5-103.0
	C_{max}	77.4	68.7-87.4

In individual patients, STI571 $AUC_{0-\infty}$ increased from 7% to 78% and the C_{max} changed from -9% to 225% when co-administered with ketoconazole.

Comments

1. The justification for setting the non-effect boundary as 0.7-1.5 has not been provided.

2. There was a significant increase in exposure to STI571 in healthy volunteers when co-administered with ketoconazole. Although healthy subjects tolerated increased STI571 exposure, caution should be taken when administering STI571 with inhibitors of the CYP3A family.

5. Drug Interaction Study Preliminary Report CSTI571 0118
Volume 1.41

Study title: An open-label, non-randomized, one-sequence crossover study to investigate the effects of STI571 on the pharmacokinetics of simvastatin in patients with chronic myeloid leukemia.

Investigators & Location:
Dr Thomas Fisher, III Dr
Stephen G O'Brien,

Report authors: Dr. Bin Peng and Dr Catherine Dutreix (Clinical Pharmacology), Dr. Renaud Capdeville (Clinical Research and Development) Novartis, Basel, Switzerland.

Study Formulation: STI571, 100mg hard gelatin capsule.

Study period: Oct. 27, 2000 to Jan. 17, 2001

Objectives:
Primary objective was to investigate the effect of the coadministration of STI571 on the pharmacokinetics of simvastatin. Secondary objective was to investigate the tolerability of STI571 alone or in combination with simvastatin.

Subjects: Twenty patients with chronic myeloid leukemia who are hematologically or cytogenetically resistant or refractory to interferon-alpha, or intolerant of, interferon-alpha entered and completed the study. This report describes only preliminary data on 9 patients.

Study Design:
This was an open-label, non-randomized, one-sequence crossover design study conducted in two centers. Each patient received an oral dose of 40 mg of simvastatin on study day 1. On days 2 – 7, each patient received 400 mg STI571 QD orally. On study day 8 an oral dose of 400 mg STI571 capsule together with 40 mg simvastatin orally was given. There was no washout phase for STI571 between treatments. It was foreseen that all patients participating in this study continued their STI571 treatment.

For each patient there was a 21-day screening period; the treatment period consisting of a baseline evaluation, the drug administration on study days 1 - 8 and a study completion evaluation 24 h after the last dosing (study day 9). Blood samples were collected at predose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hr. post dose for simvastatin and before and 24 hr. post dose for trough level of STI571.

Results:
The preliminary results showed that coadministration of STI571 increased the C_{max} of simvastatin about 2-fold and $AUC_{0-\infty}$ about 3.5-fold compared to those of simvastatin

alone. Also the half-life of simvastatin was prolonged from 1.4 to 3.2 h as shown in the following table and figures.

Table. Simvastatin PK parameters following oral administration of 40 mg Simvastatin alone and combined with oral administration of 400 mg STI571

	Simvastatin	Simvastatin plus STI571
t_{max} (h) *	1.6 (0.5 - 4.0)	1.7 (1.0 - 3.0)
C_{max} (ng/mL)	19.9 ± 21.0	37.9 ± 21.1
$t_{1/2}$ (h)	1.4 ± 0.9	3.2 ± 2.3
$AUC_{0\text{-last}}$ (ng•h/mL)	32.0 ± 25.4	121.9 ± 96.1
$AUC_{0\text{-}\infty}$ (ng•h/mL)	35.8 ± 26.3	133.1 ± 103.2
Vz/F (L)	2902 ± 2129	1657 ± 870
CL/F (L/h)	1567.3 ± 911.6	434.6 ± 216.5

all unflagged values are mean ± SD
* = median (range)

Figure. Mean plasma concentrations of simvastatin following oral administration of simvastatin alone and combined with STI571. Simvastatin 40 mg (open circles), Simvastatin 40 mg and STI571 400 mg once daily for 7 days (open squares)

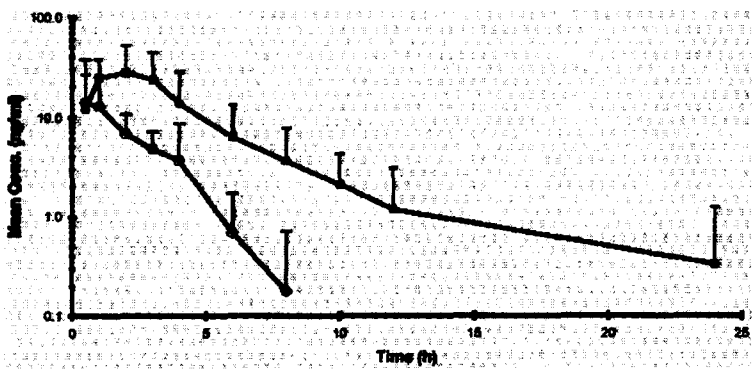
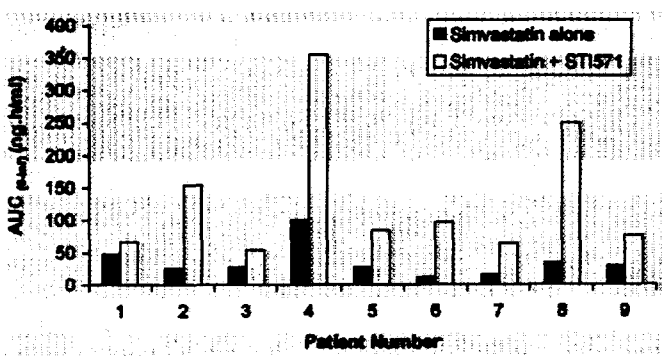


Figure. Comparison of $AUC_{0\text{-inf}}$ of simvastatin following oral administration of 40 mg simvastatin alone and combined with STI571 400 mg.



Comments:

1. Although this is a one-sequence study and there was no washout period between treatments, results showed that coadministration of STI571 increased the C_{max} of simvastatin about 2-fold (the individual data were not provided) and $AUC_{0-\infty}$ about 3.5-fold (ranged from 1.5- to 6- fold) compared to those of simvastatin alone. Also the half-life of simvastatin was prolonged from 1.4 to 3.2 h.

2. The final report should be submitted for review when it is available.

Study titles:

1. DMPK(CH) 1997/038 Metabolic stability of [C-14]CGP57148B in vitro. Species comparison using S12 liver fractions from rat, dog and man
2. DMPK(US) R99-015 Metabolism of STI571 by liver slices from human and monkey
3. DMPK(CH) 1997/564 Identification of the human cytochrome P450 isozyme(s) involved in the biotransformation of STI571 in vitro
4. DMPK(CH) R98-296 Evaluation of STI571 as an inhibitor of human P450 enzymes
5. DMPK(CH) R99-1880 Effect of STI571 on 5-fluorouracil metabolism in human liver cytosol
6. DMPK(CH) R00-963 Inhibition of the oxidative metabolism of STI571 by various comedications in human liver microsomes
7. DMPK(CH) R00-1730 Inhibition of the metabolism of [C-14]STI571 by its major oxidative metabolite CGP74588 in human liver microsomes
8. DMPK(CH) R00-1539 Inhibition of CYP2C8-dependent paclitaxel 6-alpha-hydroxylation by STI571
9. DMPK(CH) R00-1540 Effect of CGP74588 on the metabolism of P450 isozyme-specific marker substrates in human liver microsomes

Study summary and Comments:

1. Metabolism of STI571 by Liver Slices

N-desmethyl STI571 was the major metabolite produced by liver slices produced from one human liver.

2. Identification of CYP450s Associated with the Biotransformation of STI571 in Vitro

CYP3A4 is the major enzyme responsible for the biotransformation of STI571 in human liver microsome and in cDNA recombinant microsomes expressing specific CYP enzymes.

CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 played a minor role in the biotransformation of STI-571 both in the pooled liver microsomes and in the recombinant microsomes.

N-desmethyl derivative of STI571 was the major metabolite formed predominantly via CYP3A4. CYP3A5 and CYP2D6 may play a minor role in the formation of the metabolite.

P6 and P7, two minor oxidative metabolites are formed by CYP 3A4, CYP2C, CYP2D6, and CYP1A2 isoenzymes.

In pooled human liver microsomes, 65% of the biotransformation was inhibited by ketoconazole at 1 to 2 μmole/L concentrations establishing the predominant role of

CYP3A4 in the metabolism of STI571. Cyclosporin A also inhibited the formation of the metabolites with an IC_{50} value of 4.4 μmole/L at STI concentration of 25 μmole/L.

IC_{50} Values of Various Drugs in Human Liver Microsomes

Drug Names	IC_{50} (μmole/L)
Ketoconazole	< 0.5
Cyclosporin A	4.4
Erythromycin	50
Doxorubicin	63
Paclitaxel	70
Ethynylestradiol	63
Terfenadine	54
Astemizole	86
Tamoxifen	200
Carbamazepine	> 200
Warfarin	> 200
Vincristine	> 200
Prednisone	> 200
Cimetidine	> 200

STI571 concentration: 25 μmole/L.

Quinidine and Sulphaphenazole, inhibitors of CYP2D6 and CYP2C9, respectively, at 4 μmole/L concentration didn't inhibit biotransformation of STI571.

3. Inhibition of CYP450 Enzymes by STI571

Human liver microsome studies demonstrated that STI571 was a potent competitive inhibitor of CYP2C9, CYP2D6 and CYP3A4/5 with K_I values of 27, 7.5, and 8 μmole/L, respectively.

STI571 appears to be a competitive inhibitor of CYP1A2, CYP2A6, and CYP2C19 with estimated IC_{50} values of 410, 230, and 120 μmole/L, respectively.

STI571 didn't inhibit CYP2B6, CYP2E1, and CYP4A9/11.

4. Inhibition of 5-FU by STI571

In a pool of liver cytosol prepared from 10 individual donors, STI at 50 μmole/L concentration didn't inhibit metabolism of 5-FU (5 μM.) STI571 is possibly not an inhibitor of cytosolic dihydropyrimidine dehydrogenase, enzyme involved in the catabolism of 5-FU.

5. Inhibition of STI Metabolism by Various Comedications

In pooled human liver microsome, erythromycin and fluconazole inhibited the metabolism of STI571 with IC_{50} values of 50 and 118 μmole/L.

Acetaminophen, acyclovir, allopurinol, amphotericin, cytarabine, hydroxyurea, norfloxacin, and penicillin V did not inhibit metabolism of STI571 in human liver microsome.

6. Inhibition of the Metabolism of STI571 by its Major Oxidative Metabolite CGP74588

CGP74588 (N-desmethyl derivative of STI571) inhibited its own formation with a K_i value of 21 μM. The overall oxidative metabolism of STI571 was inhibited by CGP74588 with a KI value of 59 μM.

The K_M and V_{Max} values of CGP74588 formation from STI571 are 7.8 μM and 139 pmol CGP74588/min/mg.

7. Inhibition of CYP2C8 Dependent Paclitaxel metabolism by STI571

STI571 inhibited 6α-hydroxypaclitaxel formation with an IC_{50} of 99 μM at paclitaxel concentration of 7.5μM. There is a low potential for inhibition of Paclitaxel metabolism by STI571.

8. Inhibition of CYP450 Enzymes by the Major Metabolite (CGP74588) of STI571

In human liver microsome, CGP74588 inhibited CYP 3A4/5 (testosterone 6β-hydroxylation), CYP2C9 (S-warfarin 7-hydroxylation), and CYP2D6 (bufuralol 1'-hydroxylation) with K_I values of 13.7, 40.3, and 13.5 μM, respectively.

CGP74588 IC_{50} Values for Various CYP450 Enzymes

Enzymes	Specific Activity	IC_{50} (μM)	K_M (μM) for the Reaction	Substrate Concentration (μM)
CYP 1A2	Phenacetin O-deethylation	65	43	10
CYP2C8	Paclitaxel 6α-hydroxylation	99	5	7.5
CYP2C19	S-mephenytoin 4'-hydroxylation	112	5.7	24
CYP2E1	Chlorzoxazone 6-hydroxylation	NI		30

NI : No inhibition at 250 μM concentration of CGP74588

7. In vitro protein binding studies Volumes 1.32-1.33

Study titles:

1. BPK(CH)1995/116 Plasma protein binding of CGP57148 (preliminary study)
2. DMPK(F) 1998/035 In vitro blood distribution and binding of CGP57148B to plasma (or serum) proteins from human, dog, rat and cynomolgus monkey
3. DMPK(F) R99-010 In vitro blood distribution and binding of STI571 to human plasma proteins
4. DMPK(CH) R99-2582 In vitro binding of C-14 labeled STI571 to human alpha-acid glycoprotein
5. DMPK(US) R99-2667 Interspecies scaling based on a physiologically-based pharmacokinetic model

Study Summary and Comments:

1. The studies revealed concentration dependent human plasma protein binding.

Concentration in plasma	% bound	Study	Methods
µg/mL	95%	DMPK(F) 1998/035	^{14}C-label, Ultrafiltration
µg/mL	93%	DMPK(F) R99-010	^{14}C-labelled
µg/mL	91%	BPK(CH)1995/116	Ultrafiltration
µg/mL	86%	DMPK(F) 1998/035	^{14}C-label, Ultrafiltration

3. Fraction bound in erythrocytes

Concentration in plasma	% bound	Study
µg/mL	13 – 40%	DMPK(F) 1998/035
µg/mL	44%	DMPK(F) R99-010

4. Major binding proteins were albumin (30%), α1-acid glycoprotein (11%), gamma globulins (1.1%), HDL (4.7%), LDL (2.3%), VLDL (1.4%) as shown in the following

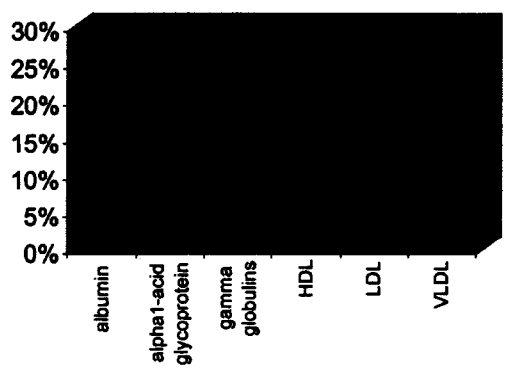


figure.

5. The protein binding of the major metabolite CGP74588 has not been studied. Therefore, the contribution of the major metabolite of STI 571, N-demethylated piperazine derivative, in the overall pharmacologic or toxic effect of Gleevec could not be assessed.

8. Food Effect Study CSTI571 0109 Extension and 0110 Amendment 2 Volume 1.38

Study title: A phase II study to investigate the effects of a fat-rich meal on the bioavailability of STI 571 and its N-desmethyl metabolite (CGS 74588) in patients suffering from chronic myeloid leukemia (CML).

Investigators & Location: Dr. Th. Fischer,

Study Formulation: STI571, 100 mg hard gelatin capsule with the following specifications.

Formulation No.	Batch No.
3752425.00.001	B990034
3752425.00.001	X3570999
3752425.00.002	X4051199

Study period: Jan. 10, 2000 to Apr. 10, 2000

Objectives: To evaluate the effect of food on the bioavailability of STI 571. The primary aims of the source studies were to determine the rate of hematological response in patients suffering from leukemia treated with STI 571 as demonstrated by a decrease in the percentage of Philadelphia (Ph) chromosome-positive cells in the bone marrow, in patients who were hematologically or cytogenetically resistant or refractory to interferon-alpha. Secondary aims included the determination of the rate and duration of complete hematological response, evaluation of the duration of complete and major cytogenetic responses, the safety profile and improvement of symptomatic parameters, the time to accelerated disease, or blast crisis and the overall survival.

Subjects: A total of 10 patients completed the study.

Study Design:

This was an open-label, one-center, crossover study carried out in 10 patients suffering from CML. The patients were participating in either study CSTI571 0109 (n=4) or CSTI571 0110 (n=6) and were randomized to either sequence A or B (A = fasted - fed and B = fed - fasted) in a two-way crossover study. On Day 8, after at least 7 days therapy with the study drug at a daily dose of 400 mg orally (p.o.), patients were hospitalized and received a 400 mg dose of STI571 either with or without the standardized high-fat containing breakfast according to randomization. During the subsequent 24 hours blood samples were collected for pharmacokinetic (PK) determinations. The patients returned on day 15 and participated in the crossover arm of the study. Blood samples (8 mL) for PK evaluations were collected prior to drug administration and at 1, 1.5, 2, 3, 4, 8, 10 and 24 hours post-dose.

The standardized high-fat meal employed in the study consisted of: 2 eggs fried in butter, 2 rashers of bacon, 4 slices of toast, 10 g butter, 20 g jam and 200 mL of whole milk

which corresponds to approximately 150 protein calories, 250 carbohydrate calories and 500-600 fat calories. Fasting conditions were defined as an overnight fast of at least 10 hours and no food was allowed for at least 4 hours post-dose.
The non-compartmental PK parameters t_{max}, C_{max}, λ_z, $t_{1/2}$, AUC_{last}, and AUC_{inf} were calculated from the plasma concentration-time profiles.

The statistical hypothesis Ho (high-fat containing meal does not change a PK parameter) versus H1 (high-fat containing meal does change a PK parameter) was tested.

Results:

Assay performance:
STI571 and CGP74588 were determined in plasma LC/MS/MS. The analyses were performed on [redacted] was carried out on [redacted] LC [redacted] column. Samples were prepared using protein precipitation with acetonitrile.

[redacted]

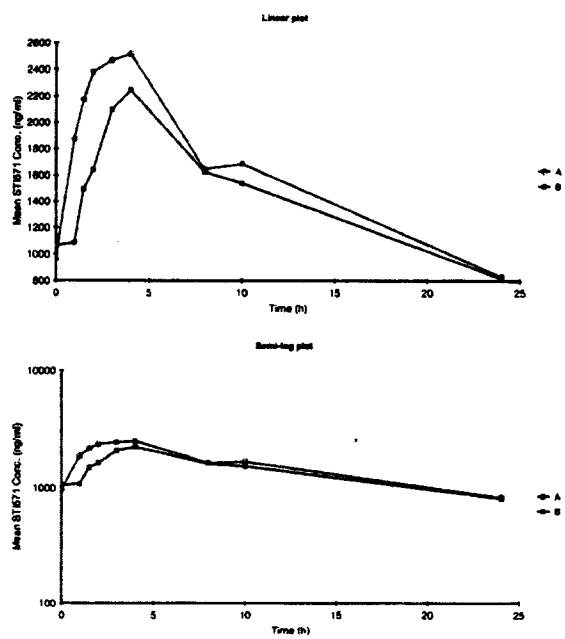
STI571

[redacted]

The precision CV% ranges exceeding [redacted]% are not acceptable.

Pharmacokinetics:
The plasma concentration profiles following administration of STI571 with or without food are shown in the following figure.

Figure **Mean plasma concentrations in CML patients following oral administration of STI571 (400 mg) with either fasted (A) or fed (B) condition**



The arithmetic means of the PK parameters for STI 571 and its N-desmethyl metabolite after administration in the fasted and fed states are summarized in the following table.

PK parameter	STI 571		N-desmethyl metabolite	
	Fasted	Fed	Fasted	Fed
t_{max} (h)	2.7 (± 1.2)	3.7 (± 0.5)	3.4(± 1.9)	4.0(± 1.6)
C_{max} (ng/ml)	2816.9 (± 1366.0)	2406.9 (± 929.1)	516.1(± 264.3)	402.5(± 118.8)
λ_z	0.05 (± 0.01)	0.04 (± 0.01)	0.02(± 0.01)	0.03(:~.01)
$t_{1/2}$ (h)	15.1 (± 5.0)	17.1 (± 4.8)	39.3(± 34.5)	30.7(± 12.6)
AUC_{0-24} (ng•h/ml)	36341.5(± 16571.9)	33220.6(± 13717.0)	8039.0(± 3540.8)	6707.9(± 1877.8)

The fed:fasted ratios for AUC_{0-inf}, AUC_{0-24}, C_{max} and corresponding 90% confidence intervals (%) derived by analysis of variance (ANOVA) for STI571 are presented in the following table.

Parameter	N	Ratio	p-Value	90% Confidence-Interval
AUC_{0-24}	10	93.0	0.4327	79.0-109.5
C_{max}	10	88.7	0.1601	76.8 – 102.4

*Ratios and confidence intervals are based on least square means for ln-transformed data.

The reviewer rechecked the calculation and the following results were obtained.

	Parameter	N	Ratio	90% Confidence-Interval
STI571	AUC_{0-24}	10	93.0	79.0-109.5
	C_{max}	10	88.7	76.8 – 102.4
CGP 74588	AUC_{0-24}	10	88.8	76.0-103.8
	C_{max}	10	84.2	70.7 – 100.3

As the tables show, when the drug was taken after consuming a fat-rich meal, t_{max} was later, AUC and C_{max} were lower and $t_{1/2}$ was longer than when the drug was taken in the fasting state for the parent drug. PK parameters for the N-methyl metabolite in the fed state showed a similar pattern except for the fed state $t_{1/2}$ which was shorter than in the fasting state. Although the calculated 90% confidence limits for AUC_{0-24} of STI571, AUC_{0-24} of CGP74588 and AUC_{0-24} of CGP74588 lie outside the range of 80-125%, the applicant concluded that the differences in PK observed after food are not of potential clinical significance. The applicant also stated that the study was underpowered to detect any difference between fed and fasting stages.

Comments:

1. The food effect study was conducted while patients were at steady state. It was difficult to observe changes in the pharmacokinetic behavior of STI571 once patients were at steady state. A better approach would have been to conduct the fed or fasted portion of the study on day 1 of the regimen or to conduct a single dose crossover

study in healthy volunteers to assess the effect of food on pharmacokinetics of STI571.

2. The active metabolite CGP 74588 should have been taken into consideration when the food effects were evaluated. Based on the reviewer's calculation, AUC_{0-24} and AUC_{0-4} of CGP74588 lie outside the range of 80-125%.

3. The assay validation results showed that the precision (CV%) ranges exceeding % that is not acceptable.

The formulation changes

The following summarizes the formulation changes during drug development:

	5mg	25mg	50mg	50mg	50mg	50mg	100mg	100mg	100mg
	3752409.00.001	3752383.00.001	3752417.00.001	3752417.00.002	3752417.00.003	3752417.00.004	3752425.00.001	3752425.00.002	3752425.00.003
STI 571									
Microcrystalline cellulose									
Crospovidone									
Silica, colloidal anhydrous/colloidal silicon dioxide									
Magnesium stearate									
Capsule contents									
Size 1, light yellow to orange yellow									
Size 1, orange to grayish orange, red inkbar									
Size 1, orange to grayish orange, red imprint NVR/SI									
Size 2, light yellow to orange yellow									
Size 3, light yellow to orange yellow									
Size 3, light yellow to orange yellow, red inkbar									
Size 3, light yellow to orange yellow, red imprint NVR/S									
Total capsule weight	130	215	240	163	163	163	304	306	306
* corresponds to 5, 25, 50 or 100mg base, respectively									

It is noted that the non-commercial formulations (3752383.00.001 and 3752417.00.001) for 25mg and 50mg strengths have been used in the clinical studies 03 001 (PK study), 0102 and 0109 (pivotal phase 2 studies).

The solubility in different pH

The pH solubility profile is shown in the following table.

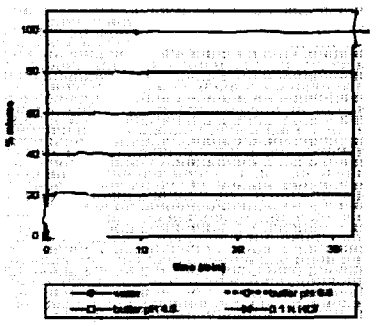
Solvent	STI571 mesylate Solubility % m/V (g/100 ml)
Buffer phosphate pH 5.5	

Selection of Dissolution Conditions

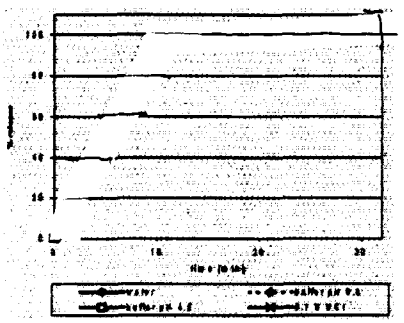
Dissolution rates of STI571 capsules were determined using the basket apparatus (USP).

Dissolution profiles were obtained under various pH conditions: pH 1, pH 4.5, pH 6.8 and in water (pH determination before and after dissolution testing) and are shown in the following Figures and Tables.

STI571 50mg Capsules, Batch X362 1199



100mg Capsules, Batch X364 1199



50 mg capsule

Dissolution in

Mean	99.4	99.5	99.6
Min			
Max			
Srel (%)			

Dissolution in

Mean	98.3	99.8	99.9
Min			
Max			
Srel (%)			

Dissolution

Mean	97.3	100.4	100.8
Min			
Max			
Srel (%)			

Dissolution in

Mean	95.4	97.8	98
Min			
Max			
Srel (%)			
pH before			
pH after			

100 mg capsule **Dissolution in**

Mean	101.8	102.8	102.8
Min			
Max			
Srel (%)			

Dissolution in

Mean	97.9	101.7	101.9
Min			
Max			
Srel (%)			

Dissolution in

Mean	94.3	99.8	100.4
Min			
Max			
Srel (%)			

Dissolution in

Mean	96.2	99.5	99.8
Min			
Max			
Srel (%)			
pH before			
pH after			

Specification
Dissolution of STI571 after — minutes: Not less than — % (Q value) of the declared content under the following conditions.

Apparatus: Basket method (Apparatus 1)
Speed: 100 rpm
Test medium: 0.1 N hydrochloric acid
Volume: 1000 mL
Temperature: 37 ± 0.5 °C

The dissolution rate method has been validated with respect to selectivity, accuracy, precision, linearity, and stability of solutions.

Replacement of dissolution testing by disintegration

The applicant proposes replacement of dissolution testing by disintegration. It is proposed to test the dissolution of the first ten STI571 50 mg and 100 mg Capsule production size batches at release. If the batch data confirm the results obtained during development, the dissolution testing will be replaced by the determination of the disintegration time according to Ph. Eur./USP for release, with the following limit: "not longer than 10 minutes". The dissolution test will be maintained for stability testing of the drug product. However, based on the ICH Guideline Q6A "Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances", replacement of dissolution testing by disintegration is allowed only when the criteria as set out in decision tree #7 of this guideline are met:

- *Rapid dissolution (> 80% in 15 minutes) at pH 1.2, 4.0 and 6.8.*
  This criterion is fulfilled.
- *High drug solubility at 37±0.5 °C throughout the physiological pH range (Dose/solubility ≤250ml at pH range 1.2-6.8).*
  STI571 mesylate is freely soluble up to pH 5.5, then, solubility reduces at higher pH values.
- *A relationship between disintegration and dissolution is determined.*
  A correlation between disintegration and dissolution data has not been determined.

Comments:

1. Based on the data provided, the dissolution specification can be set as follows.

   Not less than % (Q value) of the declared content after minutes under the following conditions.

   Apparatus: Basket method (Apparatus 1)
   Speed: 100 rpm
   Test medium: 0.1 N hydrochloric acid
   Volume: 1000 mL
   Temperature: 37 ± 0.5 °C

2. The replacement of dissolution testing by disintegration time is not appropriate based on the following.

➢ A correlation between disintegration and dissolution data has not been determined.
➢ High drug solubility at 37°C throughout the physiological pH range has not been established.

APPENDIX III. STI571 TRANSPORT STUDIES CONSULT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Service

Public Health

Food and Drug Administration
Center for Drug Evaluation and Research
Rockville, MD 20857

MEMORANDUM

Date: April 7, 2001 (revised 04/16/01)

To: Lawrence X. Yu, Ph.D.

From: Donna A. Volpe, Ph.D.

Subject: Review of Novartis STI 571 Transport Studies in Caco-2 Cell Monolayers

Purpose
Assess the permeability of STI 571 across Caco-2 cell monolayers to determine whether any efflux mechanism is involved in STI 571 transport.

Methodology

-
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-

Permeability calculations
- Standard method of apparent permeability (P_{app}) according to the equation in Artursson & Karlsson, (1991).
- Effective permeability (P_e) determined from the slope of the linear plot of the clearance volumes vs. time [Crowe & Lemaire, 1998].

Comments
- For BD Falcon™ cell culture inserts in the 24-well plate format (6.5 mm diameter), the apical and basolateral volumes would be 0.1 mL and 0.6 mL, respectively. However, in sections 3.1 and 3.2 the apical and basolateral volumes are listed as 0.5 mL and 1.5 mL, respectively, which is used in a 12-well plate format (12 mm diameter).

Format	Filter Diameter	Apical Volume	Basolateral Volume
12-well	6.5 mm	0.2 – 0.35 mL	0.7 – 0.9 mL
24-well	12 mm	0.4 – 1.0 mL	1.4 – 2.3 mL

(Source – Becton-Dickinson website [www.bdbiosciences.com/labware/Library/cellculture.html])

- In section 3.2, compound transport is described as taking place at pH 7.2 but the transport medium is prepared at pH 7.4.

Results

Compound	Concentration	P_e ($\times 10^{-6}$ cm/sec)	
		AP-to-BL	BL-to-AP
STI 571	1 μM	0.95 ± 0.18	54.8 ± 3.3
STI 571	50 μM	7.9 ± 0.52	18.2 ± 1.8
STI 571 + Cyclosporine	1 μM + 10 μM	6.3 ± 0.77	not listed
STI 571 + Verapamil	1 μM + 100 μM	10.45 ± 1.4	not listed
Mannitol	not listed	0.29 ± 0.1	not done
Propranolol	not listed	26.3 ± 1.5	not done

- There was concentration-dependent transport of STI 571 through Caco-2 cell monolayers (AP-to-BL) as the P_e for 50 μM was approximately 8-fold greater than at 1 μM. However, in the BL-to-AP direction P_e was only about 3 times greater for 1 μM than 50 μM.
- There was a difference in directional transport for STI 571, BL-to-AP transport was ~57-fold greater than AP-to-BL at 1 μM STI 571. However, this difference was greatly reduced at 50 μM.
- Cyclosporine and verapamil increased the AP-to-BL permeability of STI 571 approximately 6- and 11-fold, respectively. This indicates that STI 571 may be an efflux pump substrate, most probably P-glycoprotein.
- The authors suggest that efflux will play a limited role in the permeability of STI 571 at lower intestinal segments with "intrinsic permeability to become the rate-limiting step for *in vivo* absorption".
- Based on an estimated intrinsic permeability of approximately 1.2×10^{-6} cm/sec, the authors predict the oral absorption of STI 571 to be about 75-80%. This would be considered a low permeability drug according to the BCS Guidance.
- The authors propose that the intrinsic permeability of STI 571 "is likely to increase longitudinally along the intestine" due to its basic pK_a of ~8.

Comments

- Evaluation of several more concentrations of STI 571 would have enabled the investigators to determine whether transport was saturable. This would have given additional information on the possibility of an active transport mechanisms.
- Assessment of several pH transport conditions with STI 571 to determine if transport was actually pH-dependent as the investigators postulate.
- A high permeability standard (propranolol) and monolayer integrity marker (mannitol) were used to assess the cell model. Bi-directional transport of a know P-glycoprotein substrate would have provided information on the level of expression of efflux for comparison to STI 571.

DPQR Conclusions

STI 571 is a drug subject to efflux mechanisms and possibly active transporters. According to this specific series of experiments, STI 571 would be classified as a low permeability drug according to the BCS Guidance as its P_e is lower than its associated high permeability internal standard propranolol.

References

Artursson P, Karlsson J. Correlation between oral drug absorption in humans and apparent drug permeability coefficients in human intestinal epithelial (Caco-2) cells. Biochem Biophys Res Commun. 175(3):880-5, 1991.

Crowe A, Lemaire M. *In vitro* and *in situ* absorption of SDZ-RAD using a human intestinal cell line (Caco-2) and a single pass perfusion model in rats: comparison with rapamycin. Pharm Res. 15(11):1666-72, 1998.

G. Camenisch, J. Alsenz, H. van de Waterbeemb. G. Folkers. Estimation of permeability by passive diffusion through Caco-2 cell monolayers using the drug's lipophilicity and molecular weight. Eur. J. Pharm. Sci. 6:313-319, 1998.

Cell Culture:

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information

188-189

Pharmacometrics Review

NDA:	**21-335**
Volume:	**38 of 73 volumes**
Compound:	**Gleevec (imatinib mesylate)**
Submission Date:	**27 Feb2001 / 16 April 2001**
Applicant:	**Novartis Pharmaceuticals Corp.**
Pharmacometrics Reviewer:	**Joga Gobburu**

Aim

To establish plasma imatinib concentration (or dose) - response (desired / undesired) relationship, if possible, toward dose optimization. Specifically, the review will attempt to answer the following questions:

1) Is there a concentration/dose – time to hematologic / cytogenetic / progression response relationship?
2) Is there a concentration/dose – survival relationship?
3) Is there a concentration/dose – edema relationship?
4) Is there a necessity to adjust the dose based on the above relationships? What are the important prognostic factors?

Methods

Data

Concentration data from 3 phase II studies (110, 109 and 102) and a phase 3 study (03_001) were combined. The plasma concentrations were measured only in the US patients. The pharmacokinetics (PK) database included 550 subjects with 3941 concentrations, in total. Effectiveness and safety data from the 3 phase II studies were combined. Out of 1085 total patients in all studies, study 109 had 58 patients who were not chronic myeloid leukemia (CML) patients. Although an active metabolite, equipotent to the parent, was identified, its exposure is limited when compared that of the parent drug. Hence the data for this metabolite was not included in this analysis.

Study 102 included CML patients in blast crisis. The first 37 patients started at 400mg dose, the protocol was subsequently amended to allow higher dose and the remaining 223 patients started at 600mg dose of imatinib.

Study 109 included CML patients in accelerated phase. The first 77 patients started at 400mg dose, the protocol was subsequently amended to allow higher dosing and the remaining 158 patients started at 600 mg dose of imatinib.

Study 110 included CML patients in chronic phase. All patients were treated at a starting dose of 400 mg. In all the studies, most of patients continued to receive the starting dose through out the study.

The weight ranged between 40 to 150 kg and the age ranged between 18 to 90 years, in these patients.

Modeling

The PK data were modeled using nonlinear mixed effects technique (NONMEM, ver. 5, level 1.1). The estimation was performed using the first order conditional method with interaction between the inter-individual (IIV) and residual errors.

The exposure – WBC relationship developed by the applicant was reviewed. The time to hematologic and cytogenetic response, and survival data were modeled using Cox proportional hazard model and the severity of edema (ordinal scale), as an adverse event was modeled using logistic regression (SAS, ver 5.0, level 1.1).

Reviewer Comments on Applicant's PK and PD analyses: To be conveyed to the applicant

1. The applicant's original analysis was conducted using a data set with several formatting errors pertaining to the dosing history of the patients. During the teleconference on April 5, 2000, the applicant agreed with the FDA reviewers that there were errors in the data set. The applicant attempted to re-analyze with the corrected data. The applicant subsequently submitted a revised analysis with a revised data set. This was again amended due to similar errors as found earlier. Even this analysis is unacceptable to the Office of Clinical Pharmacology and Biopharmaceutics because of a dosing history error in **at least five subjects (NONMEM ID=9, 21, 270, 403, 535)**. A part of the data under question from the applicant's submission is shown below:

ID	STUD	DAY	TIME	AMT	DV	MDV	EVID	SS	II	SEX	AGE	WT	RACE	WBC	BWBC	CREA	SGPT	SGOT	DOSE
21	102	1	4.75	0	2.886	0	0	0	0	2	55	80.5	1	48.6	48.6	61.88	35	25	600
21	102	1	8.5	0	0.563	0	0	0	0	2	55	80.5	1	48.6	48.6	61.88	35	25	600
21	102	1	9.5	0	4.176	0	0	0	0	2	55	80.5	1	48.6	48.6	61.88	35	25	600

21	102	1	10.3333	0	6.125	0	0	0	0	2	55	80.5	1	48.6	48.6	61.88	35	25	600
21	102	1	10.9167	0	6.003	0	0	0	0	2	55	80.5	1	48.6	48.6	61.88	35	25	600
21	102	1	11.5	600	0	1	1	0	0	2	55	80.5	1	48.6	48.6	61.88	35	25	600
21	102	1	12.75	0	5.19	0	0	0	0	2	55	80.5	1	48.6	48.6	61.88	35	25	600

In the above data listing, the first sample in this patient was drawn at 4.75 hrs and the concentration of imatinib (DV) was 2.886 mg/L. The concentrations continue to be measurable and seem to be quite high till 10.9167 hrs. However, no dose appears to be given (see AMT column) till 11.5 hrs. Hence, this data set is not acceptable and the results derived thereof cannot be used to make labeling claims. The analysis presented in this review excluded data from such subjects.

2. The applicant's analysis used a model that was not well justified. A full variance – covariance matrix was estimated with out any proper mechanistic rationale. It is not clear why the random effects of the absorption constant were correlated with the random effects of clearance and volume of distribution.

3. The applicant also added dose as a covariate to describe the differences in the absorption rate constant across the population. The point estimate of the slope of the linear relationship between the dose and absorption rate constant was reported to be –0.254 with a large standard error of about 93%. Dose as a covariate is not providing reliable information and hence should be dropped.

Due to the above flaws in the applicant's analysis, the reviewer re-analyzed the data. The results are presented in the review. The aim of the reviewer's re-analysis was not only to explore the population PK but the concentration – response relationships of all the important end points.

The applicant's analysis of the exposure – WBC reduction relationship showed that almost all types of exposure measures (dose, AUC, Cmax,ss, Cmin,ss, duration above 1uM concentration) are good predictors. This analysis was based on the data collected in the study 03_001, which has a relatively wider dose range of 25 to 1000 mg. The ED50 was estimated to be about 40 mg. This translates to a concentration at steady-state of about 0.16 mg/L. Although, overall the conclusion would not change, the sponsor should consider re-evaluating the PD inhibition model that was used. The definitions of the terms do not seem to be appropriate and widely accepted. Specifically, the inhibitory Emax model has the following form:

$$WBC_{day28} = WBC_{day1} \cdot (1 - \frac{Emax \cdot Dose}{ED_{50} + Dose}) \qquad \text{(equation 1)}$$

Where, WBCday28 is the WBC count on day 28, WBCday1 is the WBC count on day 1 (baseline), Emax is the maximal fractional inhibition by the drug (has to be less than one) and ED50 is the dose required to achieve half of Emax. The equation 1 can be re-arranged as follows:

$$\frac{WBC_{day28}}{WBC_{day1}} = 1 - \frac{Emax \cdot Dose}{ED_{50} + Dose} \qquad \text{(equation 2)}$$

Equation 2 uses the ratio of WBC counts on day 28 to day 1. If one assumes that the drug completely inhibits the WBC counts, then Emax can be fixed at 1. However, the sponsor used the following equation:

$$\frac{WBC_{day28}}{WBC_{day1}} = Emax \cdot (1 - \frac{Dose}{ED_{50} + Dose}) \qquad \text{(equation 3)}$$

When there is no dose given, the right hand side equals Emax. As evident, the original definition of Emax is not valid any more!

Results and Discussion (from the reviewer's analyses)

Pharmacokinetics

CAUTION: The applicant provided the data set that was used to generate the population PK study report. Several errors, pertaining to the data format particularly the dosing history, were found in the data set by this reviewer. After several iterations of corrections, this reviewer in order to meet the review deadline used his best judgement to exclude any patients with erroneous data. Patients with NONMEM ID=21, 9, 270, 403 and 535 were found to have nonsensical dosing/concentration data and hence were removed from subsequent analyses. It is with the best belief that the other data are in place, the models developed should be interpreted.

A simple one compartment model described the PK of imatinib. Model with weight as a covariate (objective function value (OFV)=-1099.5) to describe the inter-individual variability of clearance (CL) and volume of distribution (V) performed better than that without any covariates (OFV=-1163.2). Body weight correlated with the PK parameters using the allometric equation. Body weight is known to influence CL and V, based on historic data and is seen again for this drug. A model with volume of distribution being affected by age, in a linear fashion, yielded a much better OFV of –1191 ($p<0.01$). The clinical studies included patients between 18 and 90 years of age. Imatinib possess a rather large volume of distribution of about 177 L in a 70 kg person of 50 years age. However, the slope of the age – V relationship was estimated with a large standard error and hence it was dropped from the model. Age also affected CL: higher the age slower the CL. Figure 1 shows the observed and predicted imatinib concentrations. The individual posthoc predictions are more evenly distributed about the line of identity than the population predictions, which under-

predict higher concentrations. None of the covariates (gender, race, liver enzymes) could describe the IIV further and consequently reduce the prediction bias. The final PK parameter estimates are provided in Table 1. Where available, the estimated individual PK parameters were used to predict the plasma concentrations to drive the pharmacodynamic model. Patients in whom plasma concentrations were not measured, the population typical PK parameters were employed to predict the concentrations.

Figure 1. Observed vs. population and individual posthoc predicted plasma imatinib concentrations.

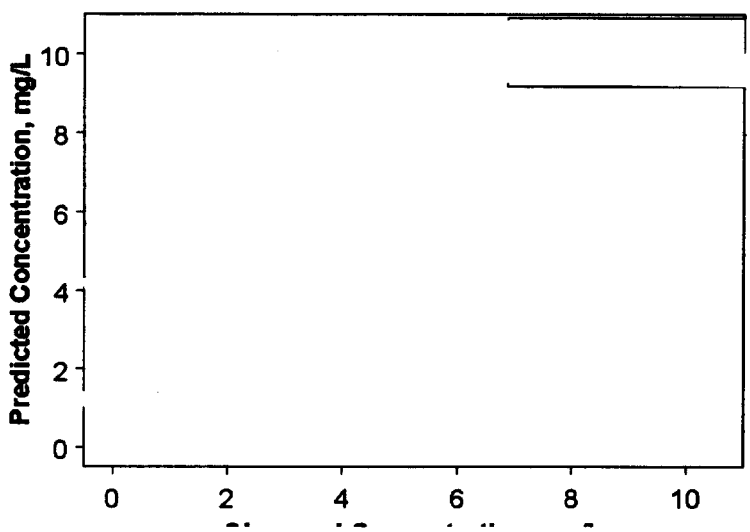


Table 1. Population PK parameter estimates of imatinib.

	CL L/h/70 kg/50yr	V L/70kg/50yr	Ka 1/h	Beta	Agecl 1/yr
Mean	10.4	213	1.05	0.746	-0.035
SE (%)	2.0	2.1	4.8	8.5	35.7
IIV (% CV)	38	37	75		
SE (%)	8.5	7.7	11.6		
CORR(CL,V)	0.768				
Residual Error	29% (proportional)	0.12 mg/L (additive)			
SE (%)	6.8	33.1			

Note: Allometric equations were used to describe the CL (beta is the exponent), V and WT relationships. A linear equation (Agecl(AGE-50)) was used to describe the relationship between age and CL with a slope of 'agecl'.*

Pharmacodynamics: Effect on WBC

The data pertaining to the WBC counts are available only during the treatment with imatinib. No data to understand the offset of the drug effect are available. Further, exact dosing history in all patients through out the study was not available. Due to these reasons, sophisticated mechanistic based modeling could not be undertaken. But descriptive statistics allowed better appreciation of the effect of the drug on WBC counts. Figure 2 shows the dose dependent decrease in the WBCs. The ED50 was found to be about 38 mg (reported by the applicant). As the shown in Table 2, the mean WBC count at the end of the study is between the mean at the beginning of the study and mean minimum during the complete study period. This suggests that WBCs significant fraction of the patients were lower than the normal range and had to probably reduce the dose and/or stop dosing for some time.

Figure 2. Time course of WBC count after the administration of imatinib.

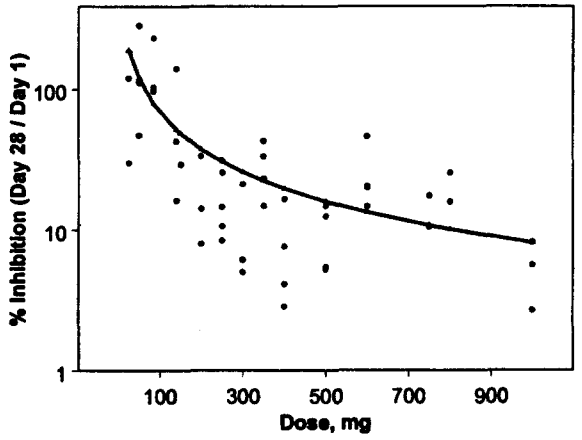


Table 2. Summary statistics of WBC counts for the different studies. The geometric means of WBCs at the beginning (BEGIN) and end (END) of the study, and minimum (MINIMUM) across the study are shown.

	WBC Counts, 10^9/L

STUDY	CML	BEGIN	END	MINIMUM
102	Chronic	24.25	10.35	1.89
109	Accelerated	16.10	7.51	1.70
110	Blast crisis	13.93	5.01	2.69

Pharmacodynamics: Survival and time to response

Figures 3, 4, 5a and 5b show the survival probability curves for the pharmacodynamic variables – survival, time to hematologic response, cytogenetic response and time to progression. Covariates such as disease state, dose, steady-state concentration, age, weight and gender were tested. For the survival end point, the only influential covariate was the disease status (i.e., whether a given patient was in the chronic, accelerated or blast crisis phase). The median survival time was estimated to be 13.47 months and 6.3 months for the accelerated and blast crisis phases, respectively. Since most of the patients in the chronic phase survived beyond the study duration, the median survival time could not be estimated. The time to hemotologic response for all the three disease states seemed to be quite comparable, with a median time to hemotologic response of about 0.8 months. The time to cytogenetic response in the chronic and accelerated phase patients differed from that in the blast crisis patients. The median time to cytogenetic response was shorter in the blast crisis patients (about 2.5 months) than the others (about 5.5 months). It appears that the severely diseased patients (blast crisis) respond to the drug faster when compared to the other patients. It should be noted that most of the patients in blast crisis phase received 600 mg while those in the chronic phase of CML received 400 mg. Hence, dose could be conceived as a confounding factor. However, the range of concentrations in both the dose groups is somewhat overlapping. The doses are only marginally apart and considering the inter–individual variability, it is almost impossible to expect different exposures at the 2 tested doses in the first place. This weakens the argument that the higher dose produces shorter times to cytogenetic response. There are other issues that relate to lack of randomization in order to get the right significance level and parameter estimates for the effect size. The design has several confounding issues for an efficient analysis to be conducted. For example, the duration since disease diagnosis seems to be longer for the patients who received 400 mg versus those who received 600mg, in study 102.

Figure 3. Survival probability of patients for the 3 different phases of CML, for the survival variable.

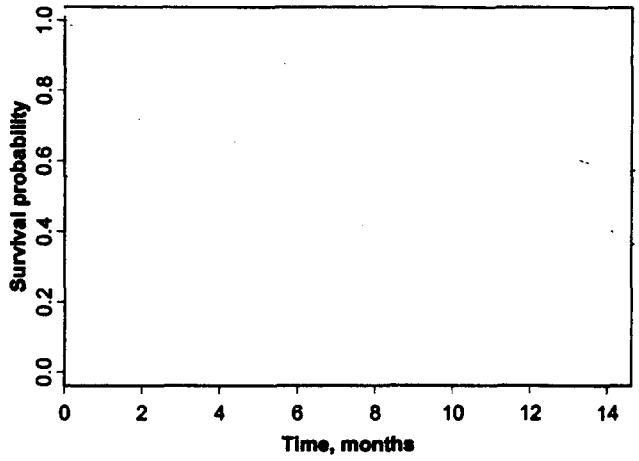


Figure 4. **Time to Hematologic Response:** Percentage of response (among responding patients) for the 3 different phases of CML.

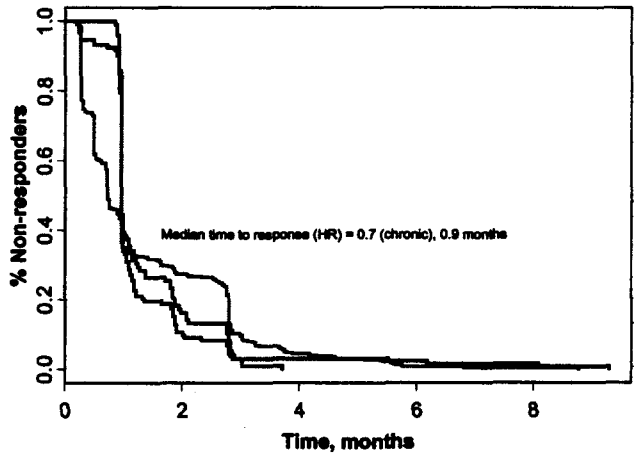


Figure 5a. **Time to Cytogenetic Response:** Percentage of response (among responding patients) for the 3 different phases of CML.

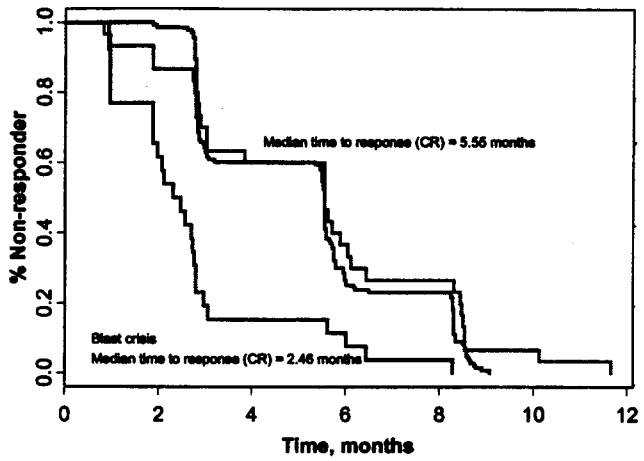
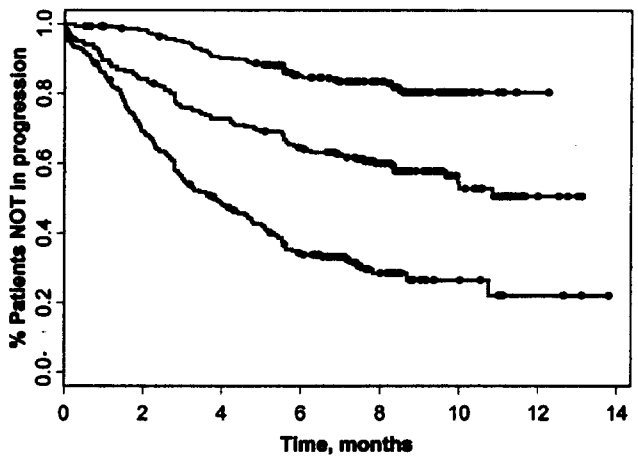


Figure 5b. **Time to Progression:** Percentage of non-responding patients for the 3 different phases of CML.



Pharmacodynamics: Edema (adverse event)

Edema, as an adverse event, observed in the patients was recorded and was given a toxicity grade on an ordinal scale ranging from 0 to 4. A grade of zero implies no edema observed, 1 implies asymptomatic (not requiring therapy), 2 implies symptomatic (requiring therapy), 3 implies symtomatic edema limiting function and

unresponsive to therapy or requiring drug discontinuation, and a grade of 4 implies anasarca (severe generalized) edema. Only one patient had a grade 4 edema, hence this patient's grade was considered as grade 3. This will not effect the conclusions about the probability of edema. Separate analysis was conducted for each of the CML disease states. Out of several covariates tested, the steady-state concentrations and age were found to influence the probability of the occurrence of edema. Higher concentrations of imatinib (in patients with accelerated or blast crisis CML) and older age increase the probability of edema. The final parameter estimates for the accelerated and blast crisis phase patients are shown in Tables 3 and 4, respectively. Figures 6 and 7 show the probability of the occurrence of edema in these 2 populations.

Table 3. Estimated parameters describing the probabilities of various grades of edema, in accelerated phase patients.

Variable	Parameter Estimate	SE	Chi-Square p-value	Odds Ratio
INTERCP1	-8.14	1.08	0.0001	.
INTERCP2	-5.36	0.84	0.0001	.
INTERCP3	-3.41	0.77	0.0001	.
CSS	0.57	0.19	0.0166	1.77
AGE	0.03	0.01	0.0236	1.03

Note: The data included only the CML patients.

Table 4. Estimated parameters describing the probabilities of various grades of edema, in blast crisis patients.

Variable	Parameter Estimate	SE	Chi-Square p-value	Odds Ratio
INTERCP1	-7.63	0.87	0.0001	.
INTERCP2	-5.60	0.78	0.0001	.
INTERCP3	-3.46	0.73	0.0001	.
CSS	0.60	0.18	0.002	1.83
AGE	0.03	0.01	0.005	1.03

Note: The data included only the CML patients.

Figure 6. Probability of a grade 3 edema occurrence in blast crisis CML patients as a function of steady – state concentration and age is shown.

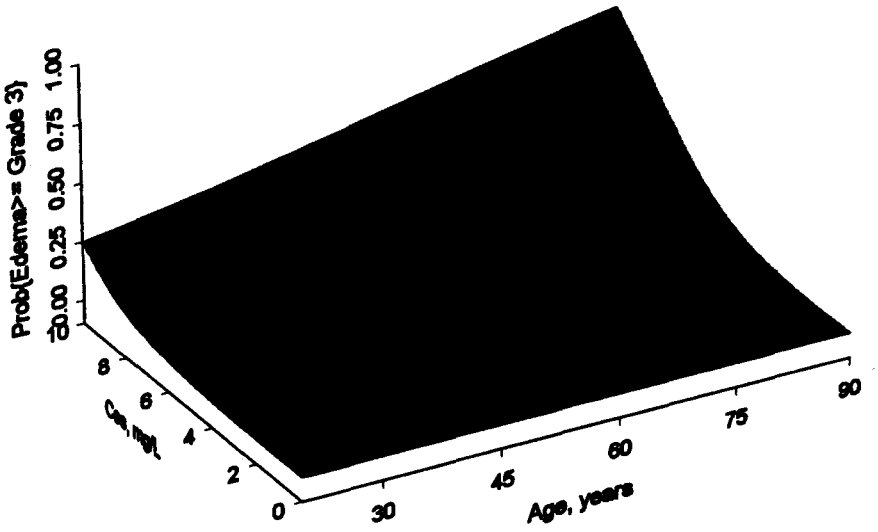


Figure 7. Cumulative probability of a grade 2 or higher edema occurrence in blast crisis CML patients as a function of steady – state concentration and age is shown.

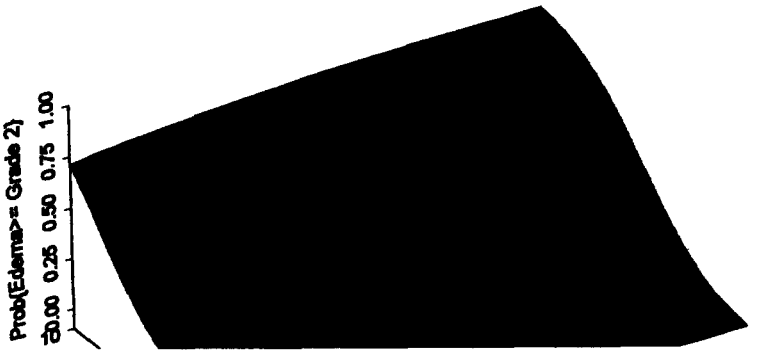


Figure 8. Probability of a grade 3 edema occurrence in accelerated CML patients as a function of steady – state concentration and age is shown.

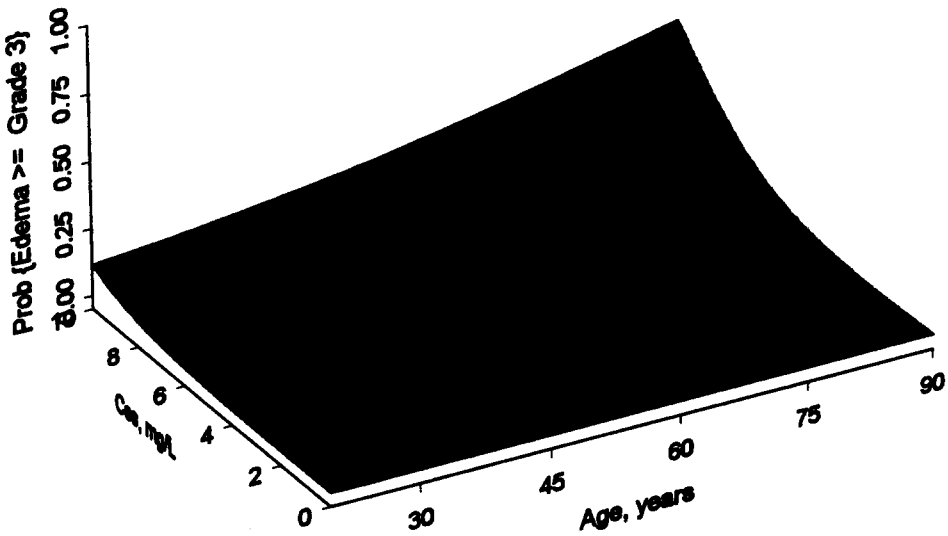
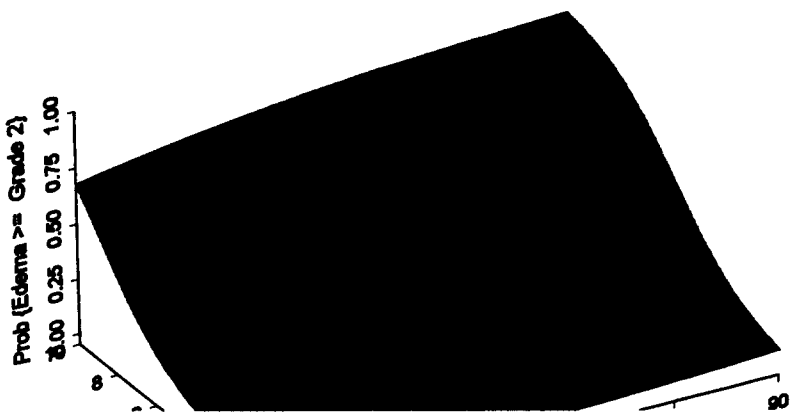


Figure 9. Cumulative probability of a grade 2 or higher edema occurrence in accelerated CML patients as a function of steady – state concentration and age is shown.



Conclusions

The answers for each of the questions raised are provided below:

Is there a concentration/dose – time to hematologic / cytogenetic response relationship?

No, the time to a hemtaologic / cytogenetic response could not be correlated with either dose or concentration. This is because of the proximity of the doses to each other. The range of the concentrations, due to the inter – individual variability, are overlapping for the 400 and 600 mg doses.

Is there a concentration/dose – survival relationship?

No, the survival of the patients could not be correlated with either dose or concentration. This is because of the proximity of the doses to each other. The range of the concentrations, due to the inter – individual variability, are overlapping for the 400 and 600 mg doses. But it is understood, through discussion with the medical reviewer, that the median survival time is longer than placebo or other currently approved treatments (from historic data).

Is there a concentration/dose – edema relationship?

Yes, there is a strong concentration – edema probability relationship. While the cost of having an edema at the benefit of having prolonged survival is considered acceptable, this information needs to be conveyed to the prescriber via labelling (see labelling recommendations below).

Is there a necessity to adjust the dose based on the above relationships? What are the important prognostic factors?

While there appears to be no concentration – clinical end point relationship, there appears to be a concentration – adverse event relationship. The fact that studies 102 (blast crisis CML patients) and 109 (accelerated CML patients) employed mostly 600 mg offers no knowledge about the effectiveness at 400 mg. The probability of having the manifestation of edema seems to be particularly important when plasma concentrations are greater than about 4 mg/L, in the elderly patients. The exposure – response curve is rather sharp from 4 mg/L onwards. The shape of the curve and the estimated parameters are comparable for the both accelerated phase and blast crisis patients. A word of caution also needs to be given when interpreting these results. The drawback of not having concentration measurements in the non-US patients was overcome by assuming that the clearance (and thus the steady – state imatinib concentrations) in these patients was similar to that of a US patient with matching body weight and age. For example, a patient in Europe who weighed 70 kg and was 50 years old was matched with a patient having similar demographics from the US population in whom PK sampling was performed. Further, the occurrence of edema was modeled by using an ordinal scale and the time course of edema was not modeled. It is possible that the patient would have been treated for edema with other drugs or the patient would have recovered without treatment. In either case, it will be interesting to investigate if the edema comes back with imatinib therapy. Nevertheless, the finding calls for some further probing into this aspect by the applicant.

The answer to whether a dosing adjustment of some sort is necessary or not, needs further elaboration. Two scenarios are considered: (1) one in which Grade 3 edema is acceptable as an adverse event and (2) another in which Grade 3 edema is not acceptable and should be minimized.

Scenario#1: When Grade 3 edema is acceptable (in the sense of 'reversibility') at the cost of having the desired effect, then all patients should start at the highest dose studied and then decrease the dose should a dose – limiting adverse event happen. But, there is no evidence in the submitted database that 600 mg is superior to 400 mg. May be a dose of 300 mg could produce equal effectiveness with a better safety profile!

Scenario#2: When Grade 3 edema is not acceptable at the cost of having the desired effect, then all patients should start at the lowest effective dose studied and then increase the dose in a manner suggested by the safety profile of the drug. All the other prognostic factors such as body weight, age and CML disease status need to be considered then to come up with individualized dosing. Also, taking one blood

sample may be necessary to ensure that the patients have concentrations below 4 mg/L. But even in this case, there is no evidence that the 400 mg is THE lowest effective dose.

Age: The influence of age diminishes at higher body weights. But at lower body weights, for example a 40 kg person who is 20 years old has a clearance of 6.58 L/h versus 5.28 L/h in a 65 year old. There is considerable change in the probability for edema (Grade 2 or higher) as evident from Figure 11.

Body weight: Figure 10 shows the distribution of concentrations in patients who received a dose of 600 mg. The distribution of the concentrations is wide spread signifying the inter – individual variability that can be expected for a fixed dose across the patients. The probability of having edema (Grade 2 or higher) is about 20% for a 50 kg person and 10% for a 100 kg person. This is just an average case. Due to the unexplained variability, these patients could have a much higher concentration (as evident from Figure 11) in which case, the probability of the adverse event increases rapidly. But the inter-individual variability does not permit for efficient dose adjustment. Therapeutic monitoring may be necessary for individualized dosing.

Figure 10. Distribution of observed concentrations from trials 102, 109 and 110 in patients who received a dose of 600 mg. The mean concentration is about 3 mg/L. Considerable number of patients had concentrations much higher than 3 mg/L.

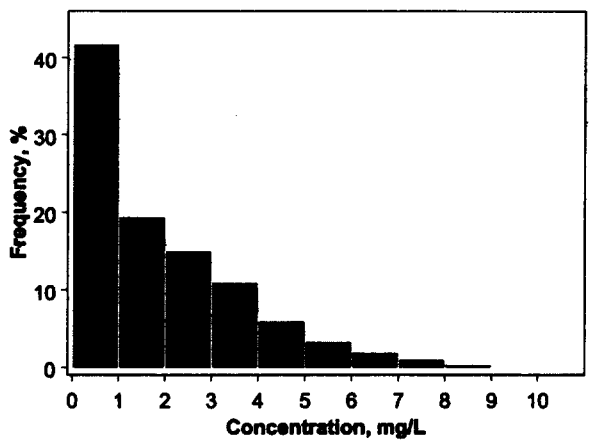
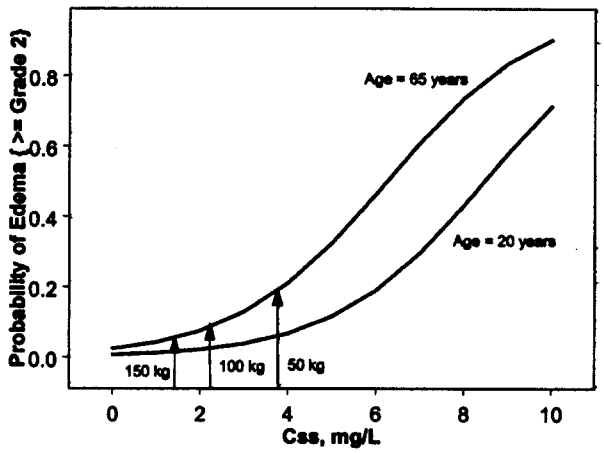


Figure 11. The influence of administering a dose of 600 mg to 3 'typical' patients with body weights 50, 100 and 150 kg. The probability of having a Grade 2 or higher edema as an adverse event doubles for the 50 kg person when compared to 100 or



150 kg person.

Labeling Recommendations

1. Applicant proposes:

<u>Recommended:</u>

Move the section to pharmacokinetics. The text should read as follows:

1 pages redacted from this section of the approval package consisted of draft labeling

Recommendation to the Applicant

The most important drawback of the submission is the lack of sound rationale for the dosing strategy. The available database does not permit derivation of an 'optimal' dose or concentration. The reviewer's analyses suggests the hypothesis that the 400 mg and 600 mg produce identical effects cannot be rejected. Further, the manifestation of edema appears to be concentration – dependent, particularly when the concentration is above ~ 4 mg/L. This aspect should be taken into account to optimize the dosing strategy of imatinib. Ongoing and future clinical trials should try to target particular concentrations below, equal to and above 4 mg/L and analyze the data to test if lower concentrations produce similar effectiveness as higher concentrations but with a better safety profile.

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/s/

Gene Williams
1/8/02 10:00:27 AM
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BIOPHARMACEUTICS

Jogarao Gobburu
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