CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-335/S-004

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21335/S-004
Drug: Gleevec
Generic Name: imatinib mesylate
Formulation: 100 mg capsules

Proposed indication: First-line Treatment for Chronic Myelogenous
                                        Leukemia (CML)

Applicant: Novartis Pharmaceutical Corporation
                                        59 Route 10
                                        East Hanover, N.J. 07936

Submission date: June 28, 2002

Reviewer: Anne Zajicek, M.D., Pharm.D.
                                        Medical Officer
                                        Office of Clinical Pharmacology and
                                        Biopharmaceutics

Pharmacometric Team Leader: Jogarao V. Gobburu, Ph.D.

Team Leader: N.A.M. Atiqur Rahman, Ph.D.

Type of submission: NDA/Supplemental

This is a review of the clinical pharmacology and biopharmaceutics studies submitted in supplement 004 to NDA 21-335 in support of a new first-line indication for adult CML.

I. Executive Summary

The applicant has submitted two studies in Section 6 (Human Pharmacokinetics and Bioavailability) of the NDA to seek approval for a new indication for Gleevec, for the first-line treatment of adults with Philadelphia chromosome positive (Ph^+) leukemia. These studies are a population pharmacokinetic (PPK) study of 371 newly diagnosed CML patients, and a drug-drug interaction study between Gleevec and rifampin, a potent inducer of the cytochrome 3A4 (CYP3A4) system in the liver. The recommended dose is 400 mg for chronic phase, and 600 mg for chronic myelogenous leukemia (CML) in the accelerated phase or in blast crisis.

A. Overall recommendations

The clinical pharmacology and biopharmaceutics information submitted in the sNDA for GLEEVEC™ is acceptable from the perspective of the Office of Clinical Pharmacology and Biopharmaceutics. The population pharmacokinetic study performed as part of this efficacy and safety trial confirms the pharmacokinetic parameter estimates in the initial NDA submission. The drug interaction study with rifampin indicates that the dosage of Gleevec should be increased by

at least 50 %, in association with close clinical monitoring, if a potent CYP3A4 inducer such as rifampin or phenytoin is coadministered.

B. Comments

The population pharmacokinetic (PPK) study was well done, and provides a large data base of pharmacokinetic (PK) and pharmacodynamic (PD) data. The rifampin study confirms the clinical suspicion that another potent CYP3A4 inducer, phenytoin, had a dramatic effect on Gleevec clearance.

C. Labeling comments regarding rifampin drug-drug interaction:

1. Applicant's proposal:

Clinical Pharmacology:

Drug interactions:

FDA recommendation:
Drug Interactions

Precautions:

/ S/
_____
Reviewer: Anne Zajicek, M.D., Pharm.D.

/S/
_____
Team Leader: N.A.M. Atiqur Rahman, Ph.D.

CC: NDA 21,335/s004
HFD-150/ Division File
HFD-150/StatenA, BrossP, JohnsonJ
HFD-860/MehtaM, SahajwallaC, RahmanNAM, ZajicekA
CDR/Biopharm

II.   Table of Contents

III. List of Abbreviations

AUC: area under the concentration vs. time curve

$AUC_{0-\infty}$: area under the concentration extrapolated from time 0 to infinity

BSA: body surface area

C_{max} : peak plasma concentration of the drug

CL: clearance

CL/F: apparent oral clearance

CML: chronic myelogenous leukemia

CV: coefficient of variation

CYP450: cytochrome P-450

GIST: gastrointestinal stromal tumor

Hr, hrs: hours

K_i: constant of inhibition

L: liter

LOD: lower limit of detection

LOQ: lower limit of quantification

M^2, m^2: square meters, meters squared

Min, min: minutes

ml, mL: milliliter

µg/L: micrograms per liter

µM: micromolar, micromoles per liter

NDA: New Drug Application

ng/ml: nanograms per milliliter

Kg, kg: kilograms

PD: pharmacodynamics

PDGF-R: platelet-derived growth factor receptor

Ph^+ : Philadelphia chromosome positive

PK: pharmacokinetics

PPK: population pharmacokinetics

$T_{1/2}$, $t_{1/2}$: half-life

t(9,22): translocation between chromosomes 9 and 22

V: volume of distribution

V_z/F: apparent volume of distribution

IV.   Summary of the clinical pharmacology findings

Imatinib mesylate is a tyrosine kinase inhibitor that has been approved for use in second line chronic myelogenous leukemia (CML) and gastrointestinal stromal tumor (GIST). This application describes a large-scale trial of adults who were newly diagnosed with CML, who were randomized to receive either imatinib or α-interferon plus cytarabine as initial therapy. As part of this study, a population pharmacokinetic (PPK) study was performed using sparse sampling (three blood samples per patient on two different treatment days). Pharmacokinetic parameters were similar to those found in the initial NDA using dense sampling. Values of pharmacokinetic parameters included: clearance of 10.0 L/hr/80 kg (CV 32 %), volume of distribution of 244.2 L/80 kg (CV 31 %), and half life of 17.1 hr.

Rifampin, when co-administered with imatinib, produced a four-fold increase in clearance and a 70 % reduction in AUC. This was not unexpected, since imatinib is metabolized by the inducible CYP3A4 family of isozymes.

V.   Background

Mechanism of action

Imatinib mesylate is a novel chemotherapeutic agent (see Figure 1, below), which binds to and inactivates the bcr-abl tyrosine kinase fusion protein produced by translocation of chromosomes 9 and 22 (t (9; 22), the Philadelphia chromosome). This mutation causes Philadelphia chromosome positive (Ph$^+$) chronic myelogenous leukemia (CML).

inhibits

tyrosine kinase

proliferation ⟺ PDGF, SCF
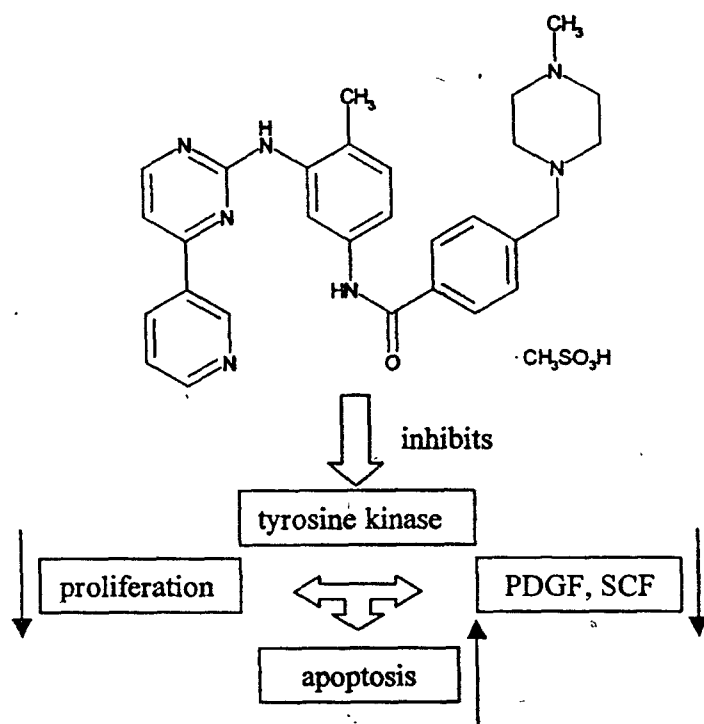
apoptosis

Imatinib also inhibits platelet derived growth factor receptor (PDGF-R) tyrosine kinase signaling. The drug also inhibits proliferation, and induces apoptosis in gastrointestinal stromal tumor (GIST) cells which express an activating c-kit mutation involved in abnormal tyrosine kinase signaling.

Imatinib was approved in 2001 by FDA for use in α-interferon (IFN)- refractory Ph^+ CML, and in early 2002 for c-kit positive GIST. It was most effective in inducing remission for patients in the chronic phase of CML (93 %), and to a lesser extent in patients with CML in the accelerated phase (37 %) or blast crisis phase (5 %). Imatinib is administered orally once or twice daily.

Common side effects include nausea, fluid retention that is occasionally severe, muscle cramps, diarrhea, vomiting, hemorrhage, fatigue, and arthralgias. There are reports of intratumoral hemorrhage in patients with GIST. In adults receiving imatinib, advanced age and edema were correlated: older patients (> 60 years old) were likely to have higher grades of edema than younger patients.

Pharmacokinetics in adults:

Absorption: Imatinib is rapidly and well absorbed, with a t_{max} of 2-4 hours, and an oral bioavailability of approximately 98 %. There appears to be dose-proportionality in the dose range of 25-1000 mg, but with a large variability (>40 %) in AUC. Absorption of a solution of imatinib had similar bioavailability to the capsule.

Distribution: Imatinib is 86-95 % protein bound, primarily to albumin and α_1-acid glycoprotein. The protein binding is concentration dependent; concentrations in plasma of 150-1500 ng/ml were 95 % bound, 4600 ng/ml was 91 % bound, 12,000-26,000 ng/ml were 86 % bound. Concentrations less than 4600 ng/ml are most relevant clinically. The volume of distribution of imatinib is large, at 213 ± 37 % (% CV) L/70 kg. The protein binding of the N-desmethyl metabolite CGP74588 is not known.

Metabolism: Clearance of imatinib is primarily by hepatic metabolism, by the cytochrome P450 (CYP) enzyme system. CYP3A4 is the specific isoenzyme which metabolizes imatinib. Clearance averaged 10.4 L/hr/70 kg, with a large interpatient variability (CV 38 %). The half-life of imatinib averages 14.3 hours.

Studies with human liver microsomes demonstrated that imatinib is a potent competitive inhibitor of CYP 2C9 (K_i 27 μM), 2D6 (K_i 7.5 μM), and 3A4/5 (K_i 8 μM). The potential therefore exists for imatinib to inhibit the metabolism of compounds metabolized by these enzymes, such as S-warfarin (2C9 substrate), desipramine (2D6), and simvastatin (3A4).

In a clinical study, imatinib increased the AUC of simvastatin by 3.5 fold. Conversely, a single dose of ketoconazole, a CYP3A4 inhibitor, increased the AUC of imatinib by 40 %. A case report indicated that phenytoin (a potent CYP3A4 inducer) co-administration produced suboptimal response to, and decreased concentrations of, imatinib; this effect was reversed when phenytoin was stopped.

There is a single active metabolite, N-desmethyl imatinib (or CGP74588), which has equal *in vitro* activity with the parent compound; however, the AUC of CGP74588 is about 16 % of the AUC of imatinib in the adults studied. Its $t_{1/2}$ is approximately 40 hours. CGP74588 inhibits its own formation with a K_i value of 21 μM, and also inhibits substrates of 2C9, 2D6, and 3A4/5.

Elimination: When ^{14}C-labeled imatinib was administered orally, 81 % of the dose was eliminated within 7 days, with 68 % excreted in the feces and 13 % in the urine. Unchanged imatinib accounted for 25 % of the dose collected (5 % in urine, 20 % in feces); CGP74588 accounted for 11 % of the dose eliminated as metabolites.

VI. Question Based Review
A. What are the population pharmacokinetics (PPK) of Gleevec ?

A randomized trial comparing α-IFN + AraC to Gleevec in 1106 adult patients with newly diagnosed CML was performed. The pharmacokinetics of imatinib were studied in 371 of the 553 patients randomized to Gleevec. The starting dose was 400 mg daily, but could be adjusted for toxicity (to 300 mg daily), or lack of response (up to 400 mg twice daily). Pharmacokinetics of imatinib and CGP74588 were determined on Day 1 and Day 29 of treatment.

Methods .

Sparse pharmacokinetic sampling was employed; samples were collected between one and three hours post dose, six to nine hours post dose, and before the next day's dose on Days 1 and 29. A PPK model was developed by the sponsor. A one-compartment model with zero-order absorption and a linear pharmacokinetics was employed as the kinetic model for a nonlinear mixed effect analysis. The model was used to assess any differences in the PK due to demographic factors (age, weight, sex, race) and time-varying laboratory values (creatinine clearance, albumin, white blood cell count (WBC), SGOT, SGPT, hemoglobin and total bilirubin).

Results

Apparent oral clearance decreased with duration of treatment. Baseline clearance was 13.8 L/h and decreased by 28 % from Day 1 to Day 29 of treatment to 10.0 L/h. Apparent volume of distribution (V_z/F) of 252 L did not change appreciably over the course of the study (252 L on Day 1 to 244.2 L on Day 29). There were large interpatient variabilities for clearance (32 %) and volume (31 %).

Both apparent clearance and volume of distribution were smaller in patients with low weight, low hemoglobin or high WBC. The effects of the covariates were considered to be small:

1. patient weight: A patient who weighed twice as much as another would have an increased clearance (⇑ 23 %) and volume of distribution (⇑ 32 %).

2. hemoglobin: A patient who had a 50 % greater hemoglobin than another would have an increased clearance (⇑ 44 %) and volume of distribution (⇑ 32 %).

3. white blood cell count: A patient with a 2/3 decrease in white blood cell count would have an increased clearance (⇑ 12 %) and volume of distribution (⇑ 8 %).

The pharmacometrics reviewer feels, due to lack of biological reasoning, that body weight is the only covariate that should be included in the final model.

B. How do the pharmacokinetic parameters of Gleevec in first-line patients compare with those of the second-line patients ?

The PPK values for clearance and volume are similar to the values from the original NDA where dense sampling was used. Table 1 below compares PK values from the current PK study with those of the original NDA. As can be seen, the clearances, volumes, and half-lives are similar.

Table 1. Comparison of pharmacokinetic parameters from original NDA (Studies 102, 109, 110) and Study 106

Pharmacokinetic Parameters	Original NDA, studies 102, 109, 110 mean (CV %)	Current sNDA Study 106 mean (CV %)
CL (L/hr/70kg)	10.4 (38 %)	10.0 (32 %)
V_{ss} (L/70 kg)	213 (37 %)	244.2 (31 %)
t ½ (hr)	14.3	17.1
N	550	371

C. Is there a PK-PD relationship ?

Edema is a prominent side-effect of Gleevec. In the initial NDA submission, there was an increased probability of edema with increasing age. A statistical exploration of edema and possible contributing factors was undertaken.

Methods (Edema)

Of the 1106 patients recruited in study 106, some patients crossed over from the interferon arm to the Gleevec arm. Excluding those crossed-over patients, a total of 551 patients, who received Gleevec, were available for characterizing the exposure-edema relationship. Missing body weights in 13 patients (of the 551 patients) were imputed with the mean body weight of 80 kg. All types of edema and multiple events were pooled together. Each patient was designated either 1, if any type of edema at any point in the trial was present, or 0, if not. Older patients and females had higher probability of edema manifestation than younger and male patients (Table 2) did.

Table 2. Exposure-edema model parameter estimates.

	Estimate	SE	P-value
Intercept	-3.1399	0.3212	<.0001
AUC	0 0321	0 00357	<.0001
Female	0.6299	0 1376	<.0001
Age	0 0318	0.00571	<.0001

The model cannot be relied upon for the following reasons.

1. Analysis of the edema data in CML patients (N=911) from the previous OCPB review (performed by Gobburu) indicated that exposure was an important predictor. Higher the exposure higher the probability of edema (grade 2 or higher). However, the current analysis showed that the trend was opposite, i.e. lower the exposure higher the chance of edema.
2. The previous analysis did not indicate that the females had higher probability of edema. There were 50% females out of 911 patients in that data base
3. The current model also indicated that the probability of edema was greater in heavier patients. The explanation of this peculiar finding us unclear, as heavier patients, given the same dose as thinner ones, will have lower AUCs. One possible explanation may be presence of lower plasma concentrations, but higher concentrations in adipose tissue, producing a second compartment out of which Gleevec slowly re-equilibrates. Additional analysis was undertaken to explore the effect of excess body weight on probability of edema; no statistical relationship was found.

According to the model predictions, females have about 88% higher probability of edema than in males. Consideration of the raw data indicates that 60% of the female patients (N=210) had edema while about 38% of male patients (N=341) had edema, in the Gleevec arm.

D. Are there any potential drug-drug interactions between imatinib and other concomitant medications?

Imatinib is metabolized by the CYP3A4 system. An early case report noted a possible drug interaction between phenytoin (a CYP3A4 inducer) and imatinib, in which a patient treated with both compounds had lower than expected imatinib concentrations and poor clinical response. Both effects were reversed when phenytoin was stopped. Study B2102 was conducted to study the effect of a CYP 3A4 inducer, rifampin, on the PK and pharmacodynamics (PD) of imatinib. The pharmacodynamic effect was change in metabolism of cortisol to 6 -β-hydroxy-cortisol; CYP3A4 induction will increase conversion of cortisol to 6-β-hydroxycortisol, both of which can be measured in the urine.

Methods:

Fourteen healthy male (n=13) and female (n=1) subjects received a single oral 400 mg dose of Gleevec on Day 1, followed by 96 hours of blood sampling for imatinib and CGP74588 pharmacokinetics. On Days 8-18, oral rifampin 600 mg daily was administered. Gleevec 400 mg was again administered on Day 15, and 96 hours of blood sampling for imatinib and CGP73488 pharmacokinetics was repeated. Urine samples for cortisol and 6-β-hydroxycortisol were collected on Day –1 (pre-Gleevec), Days 10, 14 and 18.

Assay methods:

Imatinib and CGP74588 in plasma

Imatinib and CGP74588 were analyzed by a selective _____ method (R00-1633), using _____ The dynamic range of the assay was ____ ng/ml (LOQ ___ng/ml). This method differs from the one used in the PPK study by _____ method (___ _____) and column temperature _____

Cortisol and 6-β-hydroxycortisol in urine

Urinary cortisol and 6-β-hydroxycortisol concentrations were measured by an _____method using _____ Urine samples were extracted with a ___ _____method. Quantitation limits were ___ng/ml for cortisol and ___ng/ml for 6-β-hydroxycortisol **The assay validation appears adequate.**

Statistical methods: The effect of co-administration of rifampin and imatinib and its metabolite CGP74588 was assessed by 90 % confidence intervals for the ratio of the PK parameter with the rifampin to the PK parameter with imatinib alone. An absence of a drug-drug interaction was assumed if the confidence interval fell completely in the no-effect interval of 0.75-1.33.

Results:

Figure 2 presented by the sponsor illustrates the effect of rifampin on imatinib clearance. There is a marked increase in clearance with rifampin co-administration. Table 3, also presented by the sponsor, details the specific pharmacokinetic parameters both before and after rifampin administration. Reduction in t ½, AUC_{0-24} and $AUC_{0-\infty}$ were well outside the 90 % confidence intervals, and a paired t-test showed a statistically significant change ($p<0.05$) for these PK parameters. Rifampin increased Gleevec clearance an average of four-fold ($p<0.05$)

A pronounced pharmacodynamic effect was also seen The ratio of urinary 6-β-hydroxycortisol to cortisol increased an average of 10-fold (Figure 3). Both of these results confirm the CYP 3A4-inducing effect of rifampin on Gleevec clearance.

Figure 2. Mean plasma concentration of STI571 following oral administration of Gleevec alone (A) or combined with rifampin (B)
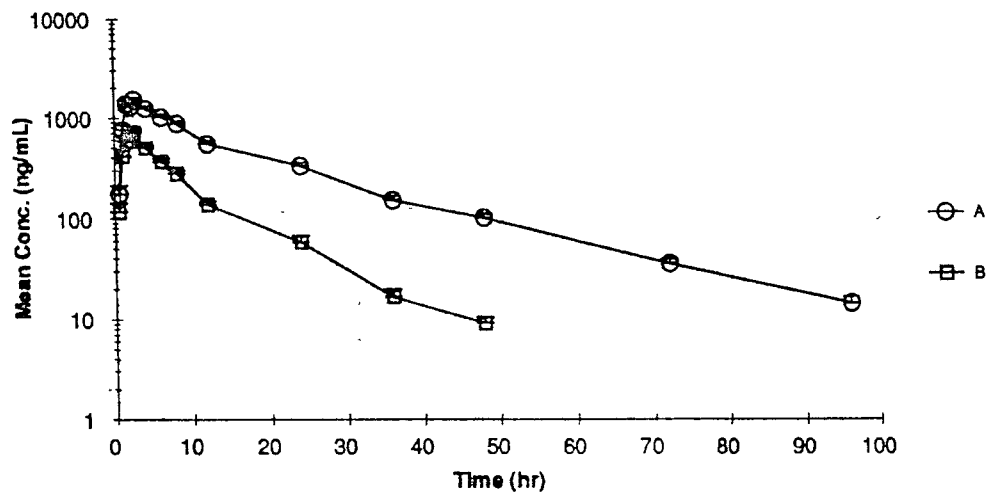
**Table 3. Imatinib PK parameters following oral administration of 400 mg Gleevec alone and combined with oral administration of 600 mg rifampin**

	Glivec plus rifampin	Glivec alone
T_{max} (h) *	2.5 (1 0 – 2 5)	2.5 (2.0 – 4.0)
C_{max} (ng/mL)	727±173	1563±285
t ½	8.8±0.7	16.7±3 1
$AUC_{(0-24)}$ (ng.h/mL)	5331±1369	16301±3475
$AUC_{(0\,inf)}$ (ng.h/mL)	5996±1631	22992±5607
V_z/F (L)	921±303	436±96
CL/F (L/h)	72.0±21 5	18.7±6.0

Figure 3. Urinary excretion of cortisol (1) and 6-β-hydroxycortisol (2) following rifampin administration on days 8-18
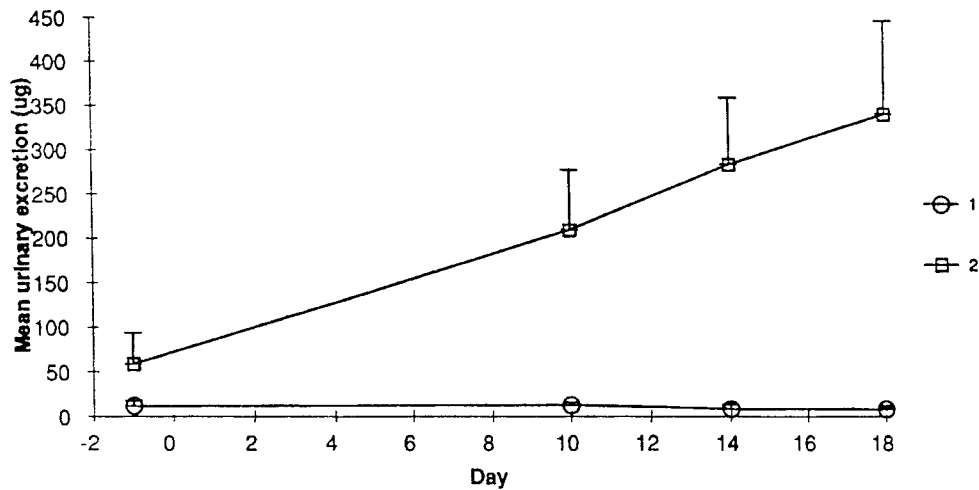
E. Is the assay valid ?

Imatinib and CGP74588 were measured by a validated ____ ——— ____method R99-1709, assay C, using ____ ——— ____The assay selectively measures parent compound and one active desmethyl metabolite CGP74588. Samples were extracted using ____ ——— _____ _____ ——— ____ tubes. The dynamic range of the assay was ____ ——— ' ng/ml for imatinib (LOQ ——— ng/ml), and ____ ——— .ng/ml for CGP74588 (LOQ ——ng/ml).

Validation is presented for the assay. The results are acceptable.

F. Are the sponsor's dosage recommendations appropriate ?

It is unclear if these dosage recommendations are appropriate, and if a lower dose could be employed in order to minimize side effects and yet have the same level of clinical efficacy As this is a life-threatening condition, it is likely preferable to err on the side of increased efficacy (which does not appear to be correlated with concentration) despite increased side-effects (which are correlated with concentration).

<p align="center">**Appendix 1. Labeling**</p>

<h1 align="center">Gleevec™ (imatinib mesylate)</h1>

<p align="center">**NDA 21-335 / S-002**
Annotated US Package Insert
New Indication: Newly Diagnosed CML</p>

Number of pages: 22

APPEARS THIS WAY
ON ORIGINAL

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

Appendix 2. Study Synopsis

Title: An open-label, single sequence, crossover study to investigate the effect of rifampin (a potent inducer of CYP450 3A4) on the pharmacokinetics of Glivec (formerly STI571)Study B2101. Rifampin interaction study

Objectives:
Primary: to investigate the effect of co-administration of rifampin on the pharmacokinetics (PK) of Glivec
Secondary: to investigate the tolerability of Glivec alone and in combination with rifampin

Study design: This study employed a single center, open-label, single-sequence, crossover design.
  Fourteen healthy male and female subjects satisfying the selection criteria for the study were to have been enrolled. Subjects who discontinued the study prematurely were to be replaced. During the first treatment period, baseline oral Glivec PK were established. The second treatment period consisted of oral Glivec PK following 8 days of oral rifampin administration. Rifampin administration was maintained throughout the PK sampling period for an additional 3 days to prevent any reduction in CYP3A4 induction. The ratio of 6-β-hydroxycortisol to cortisol excreted in the urine was measured on study days-1, 10, 14, and 18 as proof of induction of CYP3A4.
  For each subject there was a 21-day screening period; the two treatment periods, each consisting of a baseline evaluation, the drug administration and a 96-hour post-dose observation and PK sampling phase; and a study completion period 4 days after the last dosing followed by a 4 week safety period. In each of the 2 treatment periods, subjects reported to the study site 12-14 hours prior to dosing for baseline evaluations Two hours after breakfast they received either Glivec 400 mg (treatment period 1), or Glivec 400 mg + 600 mg rifampin (treatment period 2). Lunch was served 2 hours after drug administration Blood samples for determination of Glivec plasma concentrations (15 samples each treatment period) were taken for up to 96 hours after dosing. Subjects were discharged after completing the 48 hour PK sample, all samples scheduled later than 48 hours after drug administration were taken on an ambulatory basis. The end of study evaluations were to be completed 96 hours after the final dose (Day 23). Each subject was followed for an additional 4-week safety period.
Number of subjects: Fourteen subjects: 13 males, 1 female
Criteria for inclusion: Healthy, non-smoking, male and post-menopausal or sterile female subjects aged between 40 and 65 years.
Criteria for evaluation:
Safety and tolerability: Safety was assessed by recording all adverse events (AEs) reported during the course of the study, regular monitoring of clinical laboratory parameters, vital signs and ECG recordings.
Pharmacokinetics: Blood collection for STI571 plasma concentrations (5.5 mL heparin blood) was carried out predose and at 0.5, 1, 1.5, 2, 2.5, 4, 6, 8, 12, 24, 36 , 48, 72 and 96 hours post-dose (15 samples per treatment period- total 30 samples)
Analytes, media and methods: parent drug and N-desmethyl metabolite CGP74588 in plasma with a validated _____method.
PK parameters: AUC (o-infinity), AUC (0-24h), Cmax, tmax, t1/2 Cl/F, V/F from plasma concentration-time data

PK evaluations: descriptive
Urine collection: Urine was collected on Study Days -1, 10, 14, and 18 from 8:00 to 12:00 a.m.
Analytes, media and methods: Ratio of 6-β-hydroxycortisol to cortisol in urine was measured by a competitive immunoassay

Statistical methods: PK parameters (AUC $_{0-\infty}$, AUC $_{0-24}$, C $_{max}$, t$_{max}$, t $_{1/2}$, Cl/f, V/f from plasma concentration-time data)
The effects of co-administration of rifampin with Glivec were assessed by 90% confidence-intervals.
Absence of drug-drug-interaction was concluded if the 90% confidence interval around the ratio of AUC $_{0-\infty}$ (rifampin + Glivec) and AUC $_{0-\infty}$ (Glivec) fell completely within the no-effect interval of 0.75 to 1.33.

Results:
Safety and tolerability: No significant abnormalities in laboratory values, vital signs or ECG were reported. One subject had a moderate elevation of SGPT (ALT) not considered as clinically significant nor related to study drug. The co-administration of rifampin with 400mg of Glivec was well-tolerated in this study setting. Five subjects experienced adverse events which were not considered to be related to study drug. These events resolved within one to two days without sequelae.
Pharmacokinetics: Following rifampin co-administration, the mean STI571 Cmax, AUC $_{0-24}$ and AUC $_{0-\infty}$ decreased by 54% (95%-confidence interval: 48%-60%), 68% (64%-70%) and 74% (71%-76%), respectively. The increase in Cl/F was nearly 4-fold to 385.0% (348.3%-425.5%) after rifampin pretreatment. With regard to metabolites, the mean Cmax and AUC $_{0-24}$ of CGP74588 increased by 88.6% (68.3%-111.4%) and 23.9% (13.5%-35.2%) after rifampin pretreatment. However, the AUC $_{0-\infty}$ decreased by 11 7% (3.3%-19.4%).
Conclusions: A pretreatment with rifampin significantly decrease the plasma concentrations of STI571 in healthy volunteers. Concomitant use of Gleevec and rifampin or other potent inducer of CYP3A4 may result in subtherapeutic plasma levels of Gleevec.
The co-administration of rifampin with 400mg of Gleevec was well tolerated in this study setting with no safety finding identified.

Reviewer's comments: This was a well-designed study in normal volunteers, verifying the clinical importance of co-administration of a CYP3A4 inducer with imatinib. The PK and PD effects occurred in all subjects to a similar extent. It is expected that a similar degree of induction will occur in the patient population.

Appendix 3. Pharmacometrics Review
Sponsor's Analysis
XXVIII.   Methods

Of the 553 patients randomized to glivec, 371 patients were included in the pharmacokinetic analysis. Table 1 shows the demographics of the population used for the modeling.

Table 1. Demographics characteristics of the 371 patients used to develop the PK model. Frequency is provided as the number of patients of a total of 371.

	Mean	Median	Min	Max
A. Age, years	47.74	50	18	70
Weight, kg	81.81	80	40	169.5

	Frequency
Females	136
Males	235
Caucasians	326
Blacks	23
Oriental	9
Other	13

The final data set included 1930 concentration-time measurements out of which, 32% were taken up to 3 h post dose, 4% between 4 and 6 h post dose, 32% between 7 and 9 h post dose, and 31% between 22 and 27 h post dose. More than 80% of patients (n=299) had measurements at both nominal day 1 and nominal day 29. 34 Patients had measurements at nominal day 1 only, and 38 patients only at nominal day 29.

The glivec concentration-time data were fitted using a one-compartment model with zero-order absorption. As a first univariate assessment of the effect of covariates on the pharmacokinetics, each covariate was added separately to the base model. If the estimated parameter corresponding to an effect of the covariate on clearance or on volume was larger than twice the standard error, the covariate was considered as having potentially an effect on the pharmacokinetics of glivec. As a next step, all covariates were included in a full model which were identified by the univariate assessment as potentially relevant. The final model assumed a log-normal distrubution for the between-subject variability (BSV) and a combined additive and proportional variability model for the residual error.

XXIX. Results

The median glivec concentration was 1.18 mg/L and the maximum observed concentration was 7.07 mg/L. 90% of the concentrations were between 0.28 and 3.05 mg/L. The limit of

quantitation was ▬▬mg/L. The objective function value (OBJ) of the base model (simplest model without covariates) was –443.010. Inclusion of treatment phase (less than 10 days versus more than 10 days after treatment start) as covariate significantly reduced the OBJ to –503.945, i.e., at difference of about 60 compared to the base model. A change of about 10.83 is believed to yield a significance level of 0.001. The final model included body weight, hemoglobin and white blood cell count as covariates on both clearance and volume of distribution. Table 2 presents the final model parameter estimates.

Table 2. Final parameter estimates reported by the sponsor.

	Estimate	SE (%)
TVCL, L/h[a]	13.8	4
:Treatment Phase	-3.81	11
CL:Weight	0.301	32
CL:Hemoglobin	0.897	21
WBC	-0.105	33
V:BSV	32%	14
TVV, L[b]	252	3
V:Treatment Phase	-7.82	148
V:Weight	0.405	29
V:Hemoglobin	0.676	22
V:WBC	-0.07	41
V:BSV	31%	16
Corr(CL, V)	0.7	
Residual		
Proportional (CV)	26%	18
Additive (SD)	0.25 mg/L	35

[a] Individual clearance (CL) was modeled as (TRPH=1 if time>10 days),

$$CL = (TVCL + CL : TreatmentPhase \cdot TRPH) \cdot \left(\frac{Weight}{80}\right)^{CL\,Weight} \cdot \left(\frac{Hemoglobin}{130g/L}\right)^{CL\,Hemoglobin} \cdot \left(\frac{WBC}{13}\right)^{CL\,WBC}$$

[b] The covariate model for volume was similar to that for CL.

XXX. Conclusions

Based on the model, the sponsor concludes that the effects of covariates are small. A patient with a doubled weight was estimated to have an increased clearance by 23% and an increased volume of 32%. A patient with a 50% higher hemoglobin was estimated to have an increased clearance by 44% and an increased volume by 32%. A patient with reduced WBC by a factor of 3 was estimated to have an increased clearance by 12% and an increased volume by 8%. The between-subject variability was 32% for clearance and 31% for volume after adjusting for covariates.

Reviewer's Comments on Study 106 Pharmacokinetics

1. Sponsor developed the PK model methodically, screening models at each stage using loglikelihood ratio tests. The final model contains 4 covariates, namely, treatment phase (less than or greater than 10 days), weight, hemoglobin and WBC. The reviewer feels, due to lack of biological reasoning, that body weight is the only covariate that should be included in the final model. It should also be noted that there is negligible reduction in the unexplained between-subject variability in the final model compared to the model without covariates. The sponsor too notes this fact.
2. The estimates of clearance and volume are not different from those already mentioned in the current labeling. Hence no labeling changes as far as the reporting the pharmacokinetics results from this study are recommended.
3. From a pharmacometrics methods point of view, it is interesting to note that the standard error for some of the important paramters (such clearance) is only 3%. This is inconceivable taking into consideration the sparseness of the data and model uncertainty. Asymptotic standard errors might not be reliable.

Reviewer's Analysis
XXXI. Methods (Edema)

Of the 1106 patients recruited in study 106, some patients crossed over from the interferon arm to the glivec arm. Excluding those crossed over patients, a total of 551 patients, who received glivec, were available for characterizing the exposure-edema relationship. Missing body weights in 13 patients (of the 551 patients) were imputed with the mean body weight of 80 kg. Imputation by regression using age and sex as predictors of missing weight was not useful due to the large variability. All types of edema and multiple events were pooled together. Each patient was designated either 1, if any type of edema at any point in the trial was present or 0, if not. Table 3 shows the demographic characteristics of the 551 patients used for the exposure-edema modeling.

Table 3. Demographic characteristics of the patients included in the exposure-edema modeling.

	Minimum	Mean	Maximum	N
Weight, kg	40.0	79.8	169.5	1084
AUC, mg.h/L	14.1	37.0	96.2	551[a]
Age, years	18.0	48.8	70.0	1084

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Females	341
Males	210

[a] Glivec AUC was calculated for only those patients who received glivec, the AUC in other patients was assumed to be zero.

Logistic regression was used to model the exposure-edema relationship (SAS, ver. 8.2).

XXXII.   Results (Edema)

Body weight, age and sex were found to be important prognostic factors of edema. Glivec AUC was not statistically significant at an alpha of 0.05. It is interesting to find that explorative modeling efforts indicated that substituting AUC for body weight suggests that AUC is an important predictor Older patients and females had higher probability of edema manifestation than younger and male patients (Table 4).

Table 4. Exposure-edema model parameter estimates.

	Estimate	SE	P-value
Intercept	-3.1399	0.3212	<.0001
AUC	0.0321	0 00357	<.0001
Female	0.6299	0 1376	<.0001
Age	0.0318	0.00571	<.0001

The model cannot be relied upon for the following reasons:
1. Analysis of the edema data in CML patients (N=911) from the previous OCPB review (performed by Gobburu) indicated that exposure was an important predictor. Higher the exposure higher the probability of edema (grade 2 or higher). However, the current analysis showed that the trend was opposite ie., lower the exposure higher the chance of edema.
2. The previous analysis did not indicate that the females had higher probability of edema. There were 50% females out of 911 patients in that data base.
3. The current model also indicated that the probability of edema was greater in heavier patients. This is possible only if the heavier patients are more pre-disposed to edema. From an exposure point of view, in spite of the variability, the same 400 mg will produce lower concentrations in heavier patients.

Due to these confounding reasons the modeling efforts were terminated. Further, the review of studies 102, 109 and 110 indicated that the probability of edema (grade 2 or higher) was high and particularly high in the elderly patients. The labeling cautions the prescribers about this safety issue.

The odds-ratio for AUC, female and age are 1.033, 1.878, and 1.032, respectively. AUC was calculated using the individual predicted clearances from the sponsors model with weight as a covariate on clearance and volume. In patients without PK parameters, the typical clearance

predicted by the model for the given weight was used. According to the model predictions, females have about 88% higher probability of edema than in males. Body weight was not separately found as a covariate. This is most probably because of the fact that AUC is dependent on body weight. Consideration of the raw data indicates that 60% of the female patients (N=210) had edema while about 38% of male patients (N=341) had edema, in the glivec arm.

APPEARS THIS WAY
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