CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-588

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21,588
Drug:	Gleevec
Generic Name:	imatinib mesylate
Formulation:	100 mg capsule
Indication:	Philadelphia chromosome positive (Ph^+) CML in adults
Applicant:	Novartis Pharmaceutical Corporation One Health Plaza East Hanover, N.J. 07936-1080
Submission date:	December 13, 2002
Reviewer:	Anne Zajicek, M.D., Pharm.D. Medical Officer Office of Clinical Pharmacology and Biopharmaceutics
Team Leader:	N.A.M. Atiqur Rahman, Ph.D.
Type of submission:	NDA

This is a review of the bioequivalence and dissolution studies submitted in NDA 21-588 for two new formulations of Gleevec, a 100 mg scored tablet and a 400 mg tablet.

A. Executive Summary

The applicant has submitted one three-way crossover study of bioequivalence and in vitro dissolution data to seek approval for two new dosage forms of Gleevec, a scored 100 mg tablet and a 400 mg tablet. In the bioequivalence section, the mean area under the concentration time curve (AUC) and maximum concentration (Cmax) for the two new tablet dosage forms were well within the regulatory 90% confidence interval of 0.8-1.25. Dissolution of the tablets and approved capsule dosage form were similar. Dissolution specifications are:
Not less than [ ] (Q value) of the declared content after 15 minutes under the following conditions: USP paddle method (Apparatus 2), 50 rpm, 1000ml of 0.1N HCl, 37 ±5 °C.

B. 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.

C. Comments

The bioequivalence study was well done, as was the dissolution testing. The tablets appear to be bioequivalent to the capsule formulation, and the dissolution characteristics are also similar. The scored 100 mg tablet will allow more accurate pediatric dosing.

We appreciate your organized and complete submission; it was a pleasure to review the submission.

D. Labeling comments

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HOW SUPPLIED

Each film-coated tablet contains 100 mg or 400 mg of imatinib free base.

- 100 mg Tablets

Very dark yellow to brownish orange film-coated tablets, round, biconvex with bevelled edges debossed with "NVR" on one side and "SA" with score on the other side.

Bottles of 100 tablets..... NDC 0078-0401-05

- 400 mg Tablets

Very dark yellow to brownish orange film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with "NVR" on one side and "SL" on the other side.

Bottles of 30 tablets..... NDC 0078-0402-15

FDA comment: These changes are consistent with the results of this NDA.

Anne Zajicek, M.D., Pharm.D. Medical Officer Clinical Pharmacology Reviewer DPE1	N.A.M. Atiqur Rahman, Ph.D. Team Leader DPE1

CC: NDA 21,588
HFD-150/ Division File
HFD-150/StatenA
HFD-150/AShapiro, Pbross, JJohnson
HFD-860/MehtaM, SahajwallaC, RahmanA, 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-time curve 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
Kg, kg: kilograms
K_i: constant of inhibition
L: liter
LOD: limit of detection
LLOQ: 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
PD: pharmacodynamics
PDGF-R: platelet-derived growth factor receptor
Ph^+ : Philadelphia chromosome positive
PK: pharmacokinetics
PPK: population pharmacokinetics
sNDA: supplemental NDA
$T_{1/2}$, $t_{1/2}$: half-life V_z/F: apparent volume of distribution
T_{max}: time to reach maximal concentration
t(9,22): translocation between chromosomes 9 and 22
V/F: apparent volume of distribution

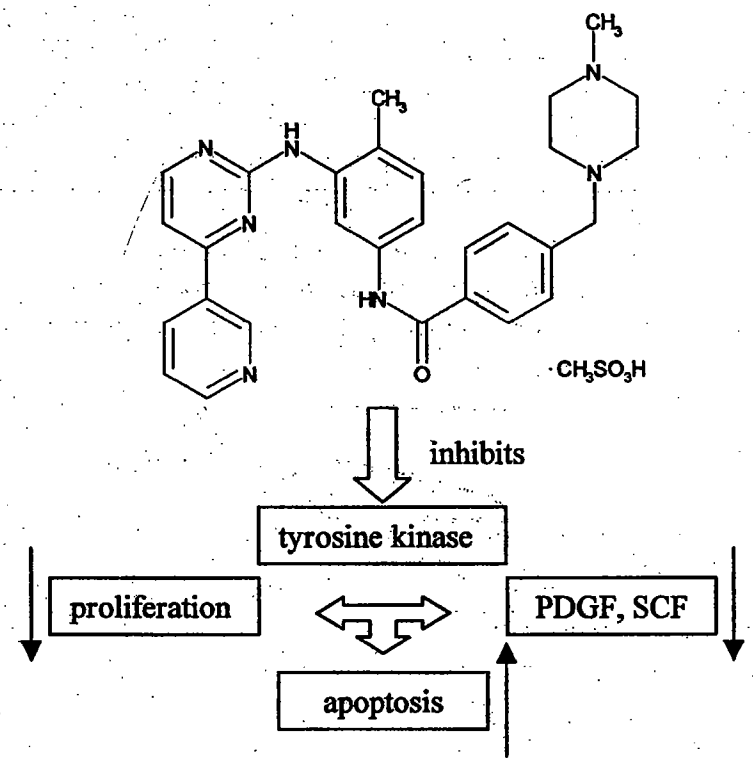
IV. Summary of clinical pharmacology findings

There were no new clinical pharmacology findings. The new tablet dosage forms have similar rate and extent of absorption as the already-approved capsule formulation. The dissolution characteristics were similar between the two tablet dosage forms and the approved capsule formulation.

V. Background

Mechanism of action

Imatinib mesylate (molecular weight 589.7, see Figure 1 below) is a novel chemotherapeutic agent, 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 lymphocytic leukemia.



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

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 the accelerated phase (37 %) and blast crisis phase (5 %).

Imatinib is administered orally once or twice daily. Common side effects include nausea, fluid retention which is occasionally severe, muscle cramps, diarrhea, vomiting, hemorrhage, fatigue, and arthralgias. In adults treated with imatinib, advanced age and edema were correlated: older patients (> 60 years old) were more 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. Relative bioavailability for a solution of imatinib compared to the intact capsule was 98.8 % (90 % confidence interval 87.7-111 %).

Distribution: Imatinib is 89-96 % 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, a concentration of 4600 ng/ml was 91 % bound, 12,000-26,000 ng/ml were 86 % bound. Concentrations less than 4600 ng/ml are the most relevant clinically; therefore, in the clinically relevant range, imatinib is 91-96% bound. Volume of distribution of imatinib is large, at 244.2 L/80 kg, with a coefficient of variation (CV) of 31 %. The protein binding of the N-desmethyl metabolite is unknown.

Metabolism: Clearance is primarily hepatic, by the cytochrome P450 (CYP) enzyme system. CYP3A4 is the specific isozyme that metabolizes imatinib. Clearance averaged 10.0 l/hr/70 kg, with a large interpatient variability (CV 32 %). The half-life of imatinib averages approximately 18 hours.

Studies with human liver microsomes demonstrated that imatinib is a potent competitive inhibitor of CYP 2C9, 2D6, and 3A4/5. 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 CYP 3A4 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 $t_{½}$ is approximately 40 hours. CGP74588 inhibits its own formation with a K_i value of 21 μM (≅12,000 ng/ml), and, like imatinib, 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. Are the two new tablet dosage forms bioequivalent to the currently-marketed 100 mg capsule?

Yes. A study was performed to investigate the bioequivalence of the two new dosage forms.

Title: "An open label, single center, three-period, three-treatment randomized crossover study to investigate the bioequivalence of a single dose of Gleevec given as a 400 mg film coated tablets and 4x100 mg film-coated tablets compared to the marketed 4x100 mg hard gelatin capsules."

Objectives:

Primary: To investigate the bioequivalence of the new dosage forms of imatinib (400 mg film-coated tablet, 4x100 mg film-coated tablets) compared to the marketed 4x100 mg imatinib hard gelatin capsules.

Secondary: To investigate the safety and tolerability of 400 mg imatinib in the form of a film-coated tablet.

Design: single center, open-label, three-treatment, three-period, randomized crossover design with 10 day wash-out period in between; subjects took drug after overnight fast, and remain fasted until four hours after the dose (see Table 3-2 below).

Table 3-2 Schematic Study Design

Screening/Pretreatment Period		**Treatment Periods**							**Post Treatment**
D-21 to D-2	Baseline Evaluation Period I D-1	Period I	Wash -out	Baseline Evaluation Period II D-1= D14	Period II	Wash -out	Baseline Evaluation Period III D-1= D28	Period III	End of Study Evaluations, after the last PK sampling of Period III + **Safety Period** (D33 to D61)
Screening evaluations		PK sampling D1-5	D6-D13		PK sampling D15-19	D20-D27		PK sampling D29-33	

Number of subjects: 30

Inclusion/Exclusion Criteria: see Appendix 1

Sampling for pharmacokinetics: 5.5 ml heparinized blood was drawn at 0 hr (pre-dose), 1, 1.5, 2, 2.5, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours post dose

Assay method: Imatinib and N-desmethyl metabolite CGP74588 were measured by a validated LC/MS/MS method with a lower limit of quantitation of 4 ng/ml for both parent compound and metabolite.

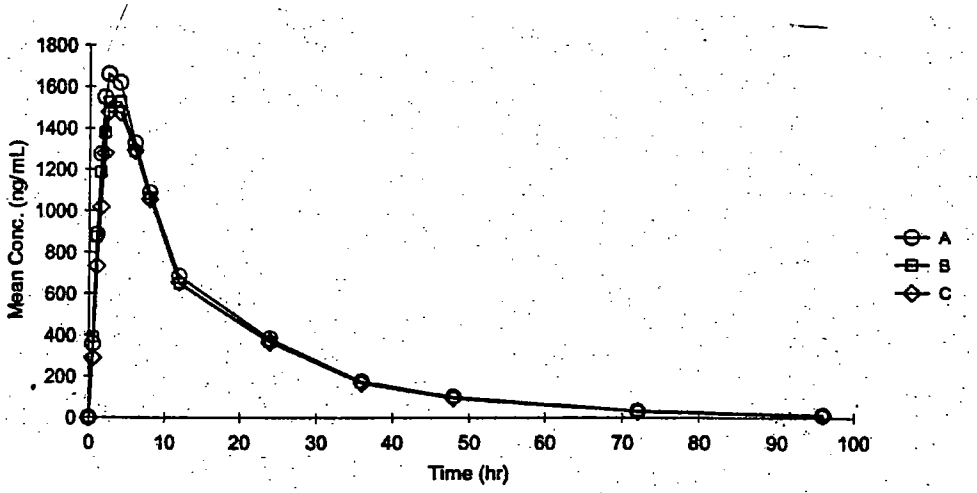
Pharmacokinetic analysis: PK parameters included $AUC_{0-\infty}$, AUC_{0-tmax}, AUC_{0-96}, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V_z/F derived from plasma concentration-time data

Total blood volume: 302.5 ml within 5 weeks

Statistical methods: Ninety percent confidence intervals for the ratio of $AUC_{0-\infty}$, AUC_{0-96}, and C_{max} were calculated. Equivalence was concluded if the confidence interval fell completely within the equivalence interval 0.8-1.25. An α-correction for multiple comparisons was made.

Results:

1. **Pharmacokinetic profiles were similar among treatment groups (see Figure 2 below, submitted by the applicant).**



A) Capsule 4x 100mg, B) tablet 4x 100mg, C) tablet 1x 400mg

AUC and Cmax for each dosage form was plotted for each patient, shown below in Figures 3 and 4.

Figure 3. Comparison of AUCs with three formulations of Gleevec

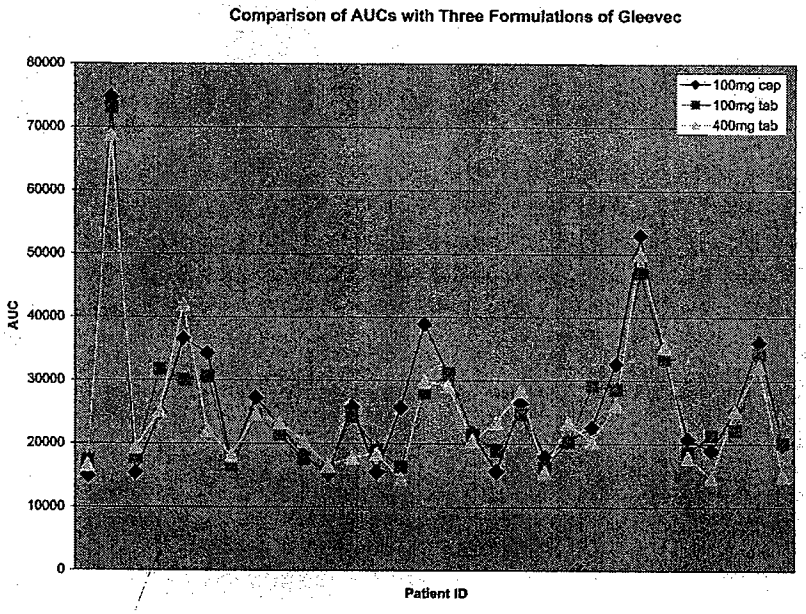
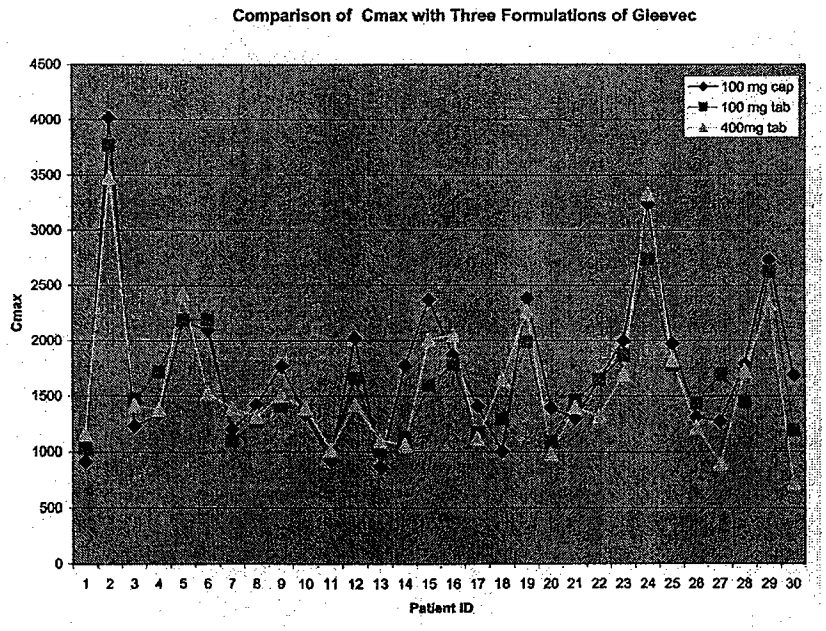


Figure 4. Comparison of Cmax with three formulations of Gleevec



1. **Pharmacokinetic parameters were calculated for each treatment group, and were found to be similar. The results are shown below in Table 7-6, submitted by the applicant.**

Table 7-6 Imatinib PK parameters following oral administration of 400mg Imatinib in the form of capsules or tablets

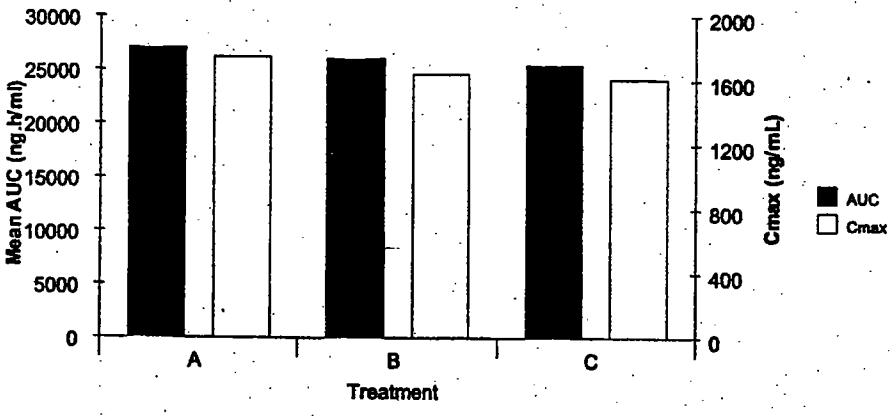
	Capsule (4x 100mg)	Tablet (4x 100mg)	Tablet (1x 400mg)
T_{max} (h) *	2.5 (2.0 – 6.0)	2.5 (1.5 – 6.0)	2.5 (1.5-6.0)
C_{max} (ng/mL)	1748±702	1638±604	1606±647
$t_{½}$ (h)	15.8±2.9	15.9±3.1	15.7±2.8
$AUC_{(0\text{-}2.5h)}$ (ng.h/mL)	2448±1198	2294±1076	2029±957
$AUC_{(0\text{-}24h)}$ (ng.h/mL)	19959±8794	19019±7684	18658±8016
$AUC_{(0\text{-}96h)}$ (ng.h/mL)	26749±12623	25724±11450	25150±11611
$AUC_{(0\text{-}Inf)}$ (ng.h/mL)	27094±12933	26081±11757	25464±11846
V_z/F (L)	383±133	387±114	404±144
CL/F (L/h)	17.1±5.8	17.3±5.1	18.0±5.7

all unflagged values are mean ± SD

* = median (range)

3. Bioequivalence is determined by similarities between AUC $_{0-\infty}$ and Cmax. Figure 7-3 below, submitted by the applicant, shows a side-by-side comparison of AUC $_{0-\infty}$ and Cmax for each treatment group.

Figure 7-3 Comparison of Mean $AUC_{(0\text{-}Inf)}$ and C_{max} of Imatinib



A) Capsule 4x 100mg, B) tablet 4x 100mg, C) tablet 1x 400mg

4. Confidence intervals for each treatment group were calculated.

Values for AUC and C_{max} were required to fall within the 90 % confidence interval of 0.8-1.25. As can be seen below (Table 7-8, submitted by the applicant), this condition was met.

Table 7-8 Statistical results

		Geometric Mean	Ratio of Geometric means	90% Dunnett adjusted CI for Ratio
$AUC_{(0\text{-}inf)}$ (ng.h/mL)	4 x 100-mg capsules	24962.3		
	4 x 100-mg tablets	24365.4	0.98	(0.91,1.04)
	1 x 400-mg tablet	23608.0	0.95	(0.89,1.01)
$AUC_{(0\text{-}96h)}$ (ng.h/mL)	4 x 100-mg capsules	24676.3		
	4 x 100-mg tablets	24063.7	0.98	(0.91,1.04)
	1 x 400-mg tablet	23334.4	0.95	(0.89,1.01)
C_{max} (ng/mL)	4 x 100-mg capsules	1632.5		
	4 x 100-mg tablets	1552.4	0.95	(0.88, 1.03)
	1 x 400-mg tablet	1502.0	0.92	(0.85,0.99)

FDA guidance recommends expressing results as the log of the geometric means. The ratio of these log-transformed geometric means must be within the 90 % confidence interval of 0.80-1.25. Table 4 shows the log-transformed means and ratios. All ratios are within the 90 % confidence interval of 0.8-1.25.

Table 4. Statistical results of log-transformed geometric means

	Log Geometric Mean	Ratio of Log Geometric Mean
$AUC_{0-\infty}$ 4x100 mg capsule	4.394	
$AUC_{0-\infty}$ 4x100 mg tablet	4.383	0.997
$AUC_{0-\infty}$ 1x 400 mg tablet	4.370	0.995
AUC_{0-96} 4x100 mg capsule	4.392	
AUC_{0-96} 4x100 mg tablet	4.375	0.997
AUC_{0-96} 1x400 mg tablet	4.368	0.995
C_{max} 4x100 mg capsule	3.209	
C_{max} 4x100 mg tablet	3.188	0.993
C_{max} 1x 400 mg tablet	3.173	0.989

B. Were the bioequivalence tests performed according to guidance?

Yes. The applicant used a replicate single-dose crossover study design in an adequate number of patients.

C. What were the results of dissolution testing?

Dissolution rates for imatinib film-coated tablets were determined using the dissolution apparatus 2, paddle. Dissolution profiles were determined under various conditions (pH 1, pH 4.5, pH 6.8 and water) at 50 rpm in 1000 ml of media at 37 °C. Both the capsule and the tablet formulations showed rapid dissolution with over [ ] of the dosage form dissolved within 15 minutes in all dissolution media (see Appendix 3). The recommended dissolution specification for these tablet dosage forms, based on the data provided, is:

> Not less than [ ] (Q value) of the declared content after 15 minutes under the following conditions: USP paddle method (Apparatus 2), 50 rpm, 1000ml of 0.1N HCl, 37 ±5 °C.

D. Were there any assay issues?

No. Imatinib and metabolite CGP74588 were measured by the same validated assay that had been used for the previously submitted NDA.

21 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Appendix 2: Inclusion/Exclusion Criteria

Inclusion criteria

- Consenting healthy male and female subjects aged 18- 65 years.
- Female subjects must have been postmenopausal or have been surgically sterilized at least six months prior to screening.
- Able to communicate well with the investigator and comply with the requirements of the study.

Exclusion criteria

- Smokers or those using any prescription or over-the-counter medications
- Participation in any clinical investigation within four weeks prior to entry or donation or loss of 400 mL or more of blood within eight weeks prior to dosing.
- Significant illness within the two weeks prior to dosing.
- History of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated).
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs or which may jeopardize the subject in case of participation in the study. The investigator should be guided by evidence of any of the following:
    - History of drug or alcohol abuse within the 12 months prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or baseline evaluations.

Appendix 3. Study Synopsis

Study synopsis

Title of study: An open-label, single center, three-period, three-treatment randomized crossover study to investigate the bioequivalence of a single dose of Glivec® (formerly STI571) given as a 400 mg film-coated tablet and 4x 100 mg film-coated tablets compared to marketed 4x 100mg Glivec® hard gelatine capsules.

Investigator: [redacted]

Publications: None

Study period: first subject dosed 29 April 2002 last subject completed 31 July 2002

Objectives:

Primary: To investigate the bioequivalence of the new dosage form of Imatinib (formerly known as STI571): 400mg film-coated tablet and 4x 100mg film-coated tablets compared to marketed 4x 100mg Imatinib hard gelatine capsules.

Secondary: To investigate the safety and tolerability of 400mg Imatinib in the form of a film-coated tablet.

Design: The study employed a single center, open-label, three-treatment, three-period, randomized crossover design. Thirty healthy male or female subjects satisfying the selection criteria for the study were enrolled. Subjects who discontinued the study prematurely were replaced. Each subject received an oral dose of 400 mg Imatinib in hard gelatine capsule form (4x 100mg) or 400mg Imatinib in the form of a single 400mg film-coated tablet or 400mg Imatinib as 4x 100mg film-coated tablets. Subjects were allocated at random to one of the six treatment sequences. There was a minimum of 10-day washout phase between treatments.

For each subject there was to be a screening period of at least 21-days; the three 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 evaluation 96 h after the last dosing followed by a four week observation safety period.

In each of the three treatment periods, subjects reported to the study site 12-14 hours prior to dosing for baseline evaluations and remained at the center for at least 24 hours post-dosing. After an overnight fast of at least 10 hours, subjects received either Imatinib 400mg as 4x 100mg hard gelatine capsules (reference treatment, "capsules"), or as a single 400mg film-coated tablet (test treatment 1, "400mg tablets") or as 4x 100mg film-coated tablets (test treatment 2, "100mg tablets"). Lunch was served not earlier than four hours after drug administration. Blood samples for determination of Imatinib plasma concentrations (15 samples each treatment period) were taken for up to 96 hours after dosing. Subjects were institutionalized until completing the 24-hour pharmacokinetic (PK) sampling; all samples scheduled later than 24 hours after drug administration were collected on an ambulatory basis. The end-of-study evaluations were completed after the last PK sampling (96 hours after the final dose). Each subject was followed for an additional four week safety period.

Number of subjects: The protocol foresaw that 30 subjects would complete the study.

Criteria for inclusion: Healthy, non-smoking, male and post-menopausal or sterile female subjects between 18 and 65 years of age who provided their written informed consent to participate in the investigation.

Investigational drug: The following table presents the batch and formulation control numbers of the medications supplied for the investigation.

Medication	Formulation No.	Batch No.
Hard gelatine capsule (100mg)	KN 3752425.00.002	X093 0700
Film-coated tablet (100mg)	KN 3762002.00.007	X039 0202
Film-coated tablet (400mg)	KN 3760311.00.011	X040 0202

Comparator drug: Not applicable.

Duration of treatment: Single doses, repeated three times and separated by washout periods of at least 10-days. Maximum duration from screening to the end of the safety period = 82 days.

Criteria for evaluation: Eligibility criteria included, inclusion/exclusion criteria, relevant medical history and current medical conditions, demography, physical examination, hepatitis screen, HIV screen, alcohol test, drug screen, urine cotinine, pregnancy test (if appropriate), drug administration and meal record, study completion information, special laboratory evaluation (genotyping of CYP2D6) and comments.

Safety and tolerability: The safety of the study drug was evaluated based on recordings of vital signs, weight, body temperature, blood pressure and pulse rate, ECG evaluation, hematology, blood chemistry and urinalysis and all adverse events (AEs).

Pharmacokinetics: Included blood collection (5.5 mL heparin blood) for assessments of Imatinib plasma concentrations, predose and at 0.5, 1, 1.5, 2, 2.5, 4, 6, 8, 12, 24, 36, 48, 72 and 96 hours post-dose. The samples were analyzed for parent drug and its N-desmethyl metabolite in plasma using a validated LC/MS/MS method. PK parameters included $AUC_{(0-inf)}$, $AUC_{(0-24h)}$, $AUC_{(0-tmax)}$, $AUC_{(0-96h)}$, C_{max}, t_{max}, $t_{½}$, CL/f, Vz/f from plasma concentration-time data.

Estimated total blood volume taken per subject: maximum 302.5 mL within approximately 5 weeks

Pharmacodynamics: Not applicable.

Statistical methods: Summary of statistics for the PK parameters are provided, together with graphical representations where appropriate.

Bioequivalence of the two tablet formulations (test treatments) to capsules (reference treatment) have been assessed by comparison of the PK parameters observed after single dose applications. Ninety percent confidence intervals for the ratio of PK parameters have been calculated ($AUC_{(0-inf)}$, $AUC_{(0-96h)}$, C_{max}). Equivalence has been concluded if the confidence interval fell completely within the equivalence interval 0.8 to 1.25. An α-correction for multiple comparisons was made.

Results:

Safety and tolerability: No clinically significant abnormalities in laboratory values, vital signs or ECG were reported. The administration of 400 mg Imatinib in hard gelatine capsule form (4x 100mg) or 400 mg Imatinib in the form of a single 400mg film-coated tablet or as 4x 100mg film-coated tablets was well-tolerated in this study setting. There were no safety concerns regarding the tolerability of Imatinib in the form of tablets or capsules.

Thirty-two mild to moderate AEs were reported in 16 of the 33 subjects during the study. Twenty-three of the AEs were not related to the study drug: fourteen were mild; nine moderate and none severe. Four subjects experienced nine AEs considered to be study drug-related: eight were mild, one moderate, and none was severe. All AEs resolved within one to two days without sequelae.

Only one subject discontinued due to mild AEs (vomiting on Day 1 and 15). These AEs resolved within a few hours without comedication or sequelae, but resulted in the subject's withdrawal from the study due to concerns that the administered drug may not have been completely absorbed.

Four subjects had moderately elevated triglyceride values on Day 14 and four subjects at the end of study (EOS). The creatinine kinase value was moderately elevated in five subjects on Day 14 and in

five subject at EOS. Minor elevation of WBC/HPF- or RBC/HPF sediment (urine) value was found in 4 subjects on Day 14 or at EOS. One subject had slightly elevated lipase value on day 14 and EOS. The Investigator did not consider any of these findings as clinically significant or related to study drug.

Pharmacokinetics:

The absorption of Imatinib after oral administration was rapid with a median T_{max} of 2.5h for both capsules and tablets. Mean $AUC_{(0\text{-}inf)}$ (27094, 26081 and 25464 ng.h/mL), C_{max} (1748, 1638 and 1606 ng/mL) and $t_{1/2}$ (15.8, 15.9 and 15.7 hr) of STI571 were similar after administration of the three oral formulations (Table below).

Imatinib PK parameters following oral administration of 400 mg Imatinib in the form of capsules or tablets

	Capsule (4x 100mg)	Tablet (4x 100mg)	Tablet (1x 400mg)
T_{max} (h)*	2.5 (2.0 – 6.0)	2.5 (1.5 – 6.0)	2.5 (1.5-6.0)
C_{max} (ng/mL)	1748±702	1638±604	1606±647
$t_{½}$ (h)	15.8±2.9	15.9±3.1	15.7±2.8
$AUC_{(0\text{-}96h)}$ (ng.h/mL)	26749±12623	25724±11450	25150±11611
$AUC_{(0\text{-}inf)}$ (ng.h/mL)	27094±12933	26081±11757	25464±11846

all unflagged values are mean ± SD

* = median (range)

For $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}96h)}$ and C_{max}, the ratio of the geometric means (test/reference) were 0.98, 0.98 and 0.95, respectively, for 4x 100mg tablets vs. 4x 100mg capsules. And for 1x 400mg tablet vs. 4x 100mg capsules for $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}96h)}$ and C_{max}, the ratio of the geometric means (test/reference) were 0.95, 0.95 and 0.92, respectively. The confidence intervals for each of these parameters were within the interval (0.80, 1.25) used for establishing bioequivalence.

Pharmacodynamics: Not applicable.

Conclusions:

Both tablet formulations (100 and 400 mg) were bioequivalent with the marketed hard gelatine capsule formulation (100mg) of Imatinib.

The administration of 400mg Imatinib in hard gelatine capsule form (4x 100mg) or 400mg Imatinib in the form of a single 400mg film-coated tablet or as 4x 100mg film-coated tablets was well tolerated in this study setting with no safety issues identified.

Date of the report: 15-November-02

Appendix 4. Dissolution Testing

Attachment E Drug Product Dissolution Testing

Dissolution profiles across the entire physiological pH-range are presented. Details on the batches are given in Attachment C (please confirm). The dissolution data were generated using USP paddle method under the following conditions:

- 0.1 N HCl (pH 1.0), rotation speed 50 rpm
  (method used for release of Glivec® film coated tablets)
- pH 4.5, rotation speed 50 rpm
- pH 6.8, rotation speed 50 rpm

The following batches have been tested:

Table E1 Batches tested

Batch no.	Strength / dosage form	Type	Formulation
X039 0202	100 mg tablets	Production batch	KN 3 762 002.007
X040 0202	400 mg tablets	Production batch	KN 3 760 311.011
X093 0700	100 mg capsules	Production batch	KN 3 752 425.002

The results and dissolution profiles of Glivec® capsules (batch X093 0700), and film-coated tablets (100 mg batch X039 0202 and 400 mg batch X040 0202) obtained at the different pH conditions, are presented in tables E2-E4 and figures E1-E3 respectively.

Table E2 **Dissolution in 0.1 N HCl / 50 rpm**

Testing conditions	Batch		Dissolution [% of declared content] after 5 min.	10 min.	15 min.	20 min	30 min.
tablet 400 mg n=12	X040 0202	mean	48.2	91.4	97.4	97.8	98.3
		min.	[				
		max.					
		Srel (%)					]
tablet 100 mg n=12	X039 0202	mean	46.1	92.9	94.6	95.6	96.4
		min.	[				
		max.					
		Srel (%)					]
capsule 100 mg n=6	X093 0700	mean	84.4	88.4	90.3	91.4	93.1
		min.	[				
		max.					
		Srel (%)					]

Figure E1 **Dissolution in 0.1 N HCl / 50 rpm**

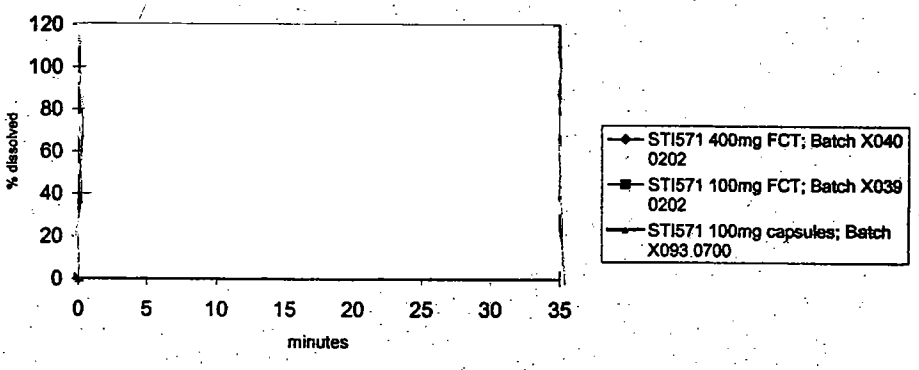


Table E3	Dissolution at pH 4.5 / 50 rpm						
Testing Conditions	Batch		Dissolution [% of declared content] after				
			5 min.	10 min.	15 min.	20 min	30 min.
tablets 400 mg n=12	X040 0202	mean	48.9	88.5	93.7	94.3	94.8
		min.					
		max.					
		Srel (%)					
tablet 100 mg n=12	X039 0202	mean	46.5	90.1	93.5	95.0	96.3
		min.					
		max.					
		Srel (%)					
Capsule 100 mg n=6	X093 0700	mean	75.1	88.1	90.5	91.7	93.1
		min.					
		max.					
		Srel (%)					

Figure E2 **Dissolution at pH 4.5 / 50 rpm**

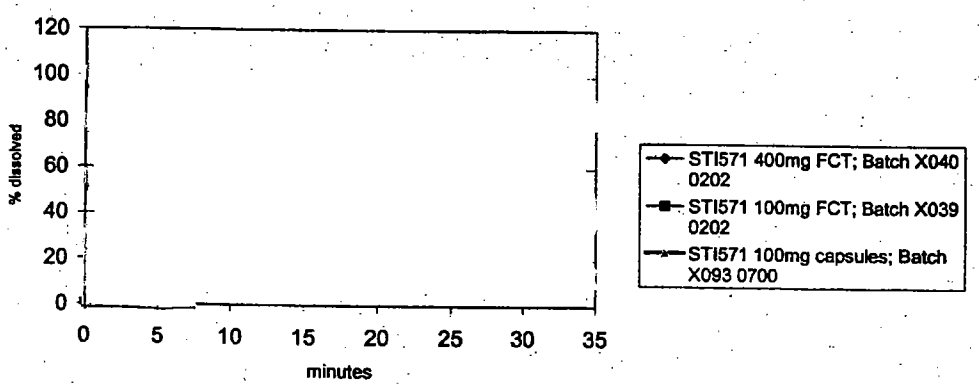
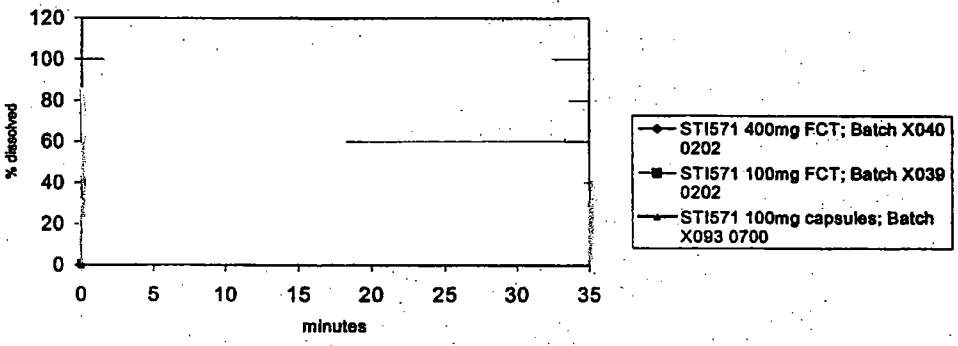


Table E4 Dissolution at pH 6.8 / 50 rpm

Testing conditions	Batch		Dissolution [% of declared content] after 5 min.	10 min.	15 min.	20 min	30 min.
tablet 400 mg n=12	X040 0202	mean	44.6	82.4	91.6	92.1	92.4
		min.					
		max.					
		Srel (%)					
tablet 100 mg n=12	X039 0202	mean	39.4	90.3	94.0	95.8	97.6
		min.					
		max.					
		Srel (%)					
capsule 100 mg n=6	X093 0700	mean	69.7	83.7	86.9	89.3	90.9
		min.					
		max.					
		Srel (%)					

Figure E3 Dissolution at pH 6.8 / 50 rpm



The dissolution profiles of the capsules 100 mg, film-coated tablets 100 mg and film-coated tablets 400 mg are rapid and similar to each other over a pH range of 1.0 to 6.8, as shown by the fact that both capsules and tablets release more than [ ] of the labeled amount of the drug substance within 15 minutes.

Appendix 5.

Attachment F Proposed Dissolution Method and Specification

[ ]

Specification	
Dissolution of imatinib mesylate after 15 minutes:	Not less than [ ] (Q value) of the declared content according to acceptance table of USP (levels 1 and 2 only)
Principle	Measurement of the amount of drug substance released in a dissolution apparatus 2 (paddle) according to Ph. Eur. or USP
Reagents	
Hydrochloric acid	0.1 M
Dissolution conditions	Paddle method according to Ph. Eur. 2.9.3, "Dissolution Test for Solid Dosage Forms" or USP <711>, "Dissolution"
Speed of rotation	50 ± 2 rpm
Test medium	0.1 M hydrochloric acid.
Volume of test medium	1000 ml
Temperature of test medium	37 ± 0.5 C
Number of units tested	Examine the prescribed units according to the acceptance table of USP
Procedure	
Note	[

[ ]

[ ]

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