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# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# NDA 21-335/S-001

# Clinical Pharmacology and Biopharmaceutics Review

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS NDA REVIEW

**Product name and generic name:** Gleevec®, imatinib
**Type of dosage form and strength(s):** 50 & 100 mg capsules
**Indication(s):** GIST (gastro-intestinal stromal tumor)
**NDA number, type:** supplement to NDA 21-335, 505(b)(1), 1P
**Applicant name:** Novartis Pharmaceuticals Corporation
**Submission dates (letter dates):** October 15, 2001
December 7, 2000
**OCPB and ORM Division names:** DPE I and DODP
**OCPB Reviewer(s) and Team Leader names:**
Primary Reviewer: Gene M. Williams, Ph.D.
Team Leader for Primary Reviewer: N.A.M. Rahman, Ph.D.
Pharmacometrics Reviewers: Gene M. Williams, Ph.D., Gabriel Robbie, Ph.D.
Team Leader for Pharmacometrics Reviewers: Jogarao Gobburu, Ph.D.

## *I. Executive Summary*

### *A. Recommendations*

The Clinical Pharmacology and Biopharmaceutics information provided in this NDA is acceptable. There are no clinical pharmacology-based risk management recommendations.

The following comments are being conveyed to the Applicant.

Relevant to the population pharmacokinetics analysis:

1. Due to the lack of biological plausibility of the identified covariates, the Applicant's final model cannot be accepted. For regulatory decision making purposes, the sponsor is encouraged to consider only mechanistically relevant covariates during model building. The Pharmacometrics group at the Office of Clinical Pharmacology and Biopharmaceutics, CDER, FDA, welcomes scientific discussions with sponsors on model building strategies both at the protocol stage as well as during modeling.

2. Patient NONMEM ID=13 was not considered to be at steady-state even after 873 h post dosing, as per the data submitted to the agency. The reason for this is not clear.

### *B. Phase IV Commitments*

None.

## *II. Table of Contents*

## *III. Summary of Clinical Pharmacology and Biopharmaceutics Findings*

Gleevec was approved on May 10, 2001, under accelerated approval regulations, for the treatment of chronic lymphoid leukemia (CML). The current supplemental NDA seeks approval for treatment of Gastro-Intestinal Stromal Tumor (GIST). The DODP has indicated that, should the drug be approved, it will be under accelerated approval regulations.

This NDA supplement contains a single new study. This study examines the pharmacokinetics of imatinib in a subset of GIST patients that were studied for efficacy and safety. The pharmacokinetics data is 19 full profiles and 54 sparse profiles and was analyzed using NONMEM. The Reviewer recommends that a labeling statement that pharmacokinetics are similar between CML and GIST patients be added to the package insert.

Two additional studies have been "co-packaged" with the NDA. The more relevant to the current NDA is a completed study report for a drug interaction study of the effect of imatinib of the pharmacokinetics of simvastatin. The effect of imatinib on simvastatin pharmacokinetics was described in the original NDA (preliminary study report of the current final study report) for Gleevec and is included in the current Gleevec label. The submitted final study report affirms the prior conclusion that imatinib increases simvastatin exposure (approximately a 2-fold increase in Cmax and 3.5-fold increase in AUC). The final study includes a description of imatinib pharmacokinetics in Japanese CML patients. Although the study is small and an analytical methods report for the study is lacking, there appears to be no significant difference between pharmacokinetics in Japanese relative to other groups.

## *IV. Question-Based Review*

### *A. General Attributes*

*What are the highlights of the chemistry, biopharmaceutics and efficacy and safety information of the drug product?*

see review of NDA 21-335 for CML – Appendix E.

### *B. General Clinical Pharmacology*

*What are the pharmacokinetic and pharmacodynamic properties of the drug substance?*

see review of NDA 21-335 for CML – Appendix E.

### *C. Intrinsic Factors*

*What intrinsic factors influence exposure and/or response and should this information be used to change the package insert?*

The following intrinsic factors, and no others, have been examined in the current NDA or in the studies submitted concurrently with the current NDA: age, gender, weight, daily dose, creatnine, total WBC count, SGOT, SGPT, albumin, bilirubin, hemoglobin, presence of liver metastases, edema, ethnicity (a study in Japanese CML patients has been submitted) and disease (a comparison between GIST and CML patients is made).

With the exception of ethnicity and disease, the ability of intrinsic factors listed above to account for differences in clearance and volume was performed by the Applicant in a population PK analysis. A full review of this analysis is included in Appendix C. of this review. Below is a summary of the full review.

The following covariates were tested: age, gender, weight, daily dose, creatnine, total WBC count, SGOT, SGPT, albumin, bilirubin, hemoglobin, presence of liver metastases, and edema. Four covariates were statistically significant: clearance increased as a function of albumin and decreased as a function of white blood cell count while volume of distribution increased as a function of albumin and decreased as a function of bilirubin.

The Reviewer can offer no mechanistic explanation for the observed ability of the significant covariates to account for between-individual differences. Similarly, the Applicant offers no explanation. This lack of mechanistic support increases a typical concern for population pharmacokinetic analyses: significance of the covariate effects may have resulted from chance (multiplicity of covariates tested resulting in false positives) rather than a true effect.

The effect of the covariates, relative to the total inter-individual variability in the parameters, is not pronounced: incorporation of the covariates reduces %CV of clearance from 50% to 41% and %CV of volume from 47 to 39%.

Based on the lack of mechanistic underpinning, the relative ineffectiveness of the covariates in accounting for inter-individual variability, and the current lack of a known relationship between imatinib concentration and effectiveness and safety, the Reviewer concludes that the current analysis does not indicate that dose should be modified as a function of albumin, bilirubin or white blood cell count. This agrees with the conclusions of the Applicant: the Applicant has not suggested dose modification based upon the identified covariates.

The effects of two other intrinsic factors on pharmacokinetics are included in the NDA. The first is disease: the Applicant has produced a table which shows a comparison of pharmacokinetics between GIST and CML patients. This Table is reproduced below (from p. 6-13 of Item 6 of the current NDA)

**APPLICANT'S TABLE 3.2:**

**Table 3-2. Comparison of PK parameters at steady state in patients with GIST and CML**

| | 400 mg | | 600 mg | |
|---|---|---|---|---|
| | GIST(n=10) | CML(n=5) | GIST(n=6) | CML(n=9) |
| Cmax (ng/ml) | 3950±1280 | 2595±787 | 4360±2150 | 3509±1649 |
| $T_{1/2}$ (h) | 25.0±29.3 | 19.3±4.4 | 21.0±6.7 | 15.6±5.0 |
| AUC (0-24) (µg.h/ml) | 60.9±24.7 | 40.1±15.7 | 75.4±31.4 | 51.7±26.7 |
| Vz/F (L) | 230.7±177.6 | 295.0±62.5 | 272.2±109.8 | 296.9±102.5 |
| Cl/F (L/h) | 8.13±4.67 | 11.2±4.0 | 9.5±4.8 | 14.4±6.8 |

Source: [2222] appendix 8.1 and original NDA [03 001] appendix 8.1.1

These data show a trend toward an increased exposure in GIST patients relative to CML patients. The Applicant concludes that a definitive conclusion of higher exposure in GIST cannot be made (due to the variability present), but that the observed differences may be attributable to GIST patients having increased hepatic abnormalities relative to CML patients. The Applicant has not proposed any changes to the label indicating a PK difference between the two disease populations. The Reviewer believes that the differences are a function of variability rather than a true difference between the two populations. This conclusion is based upon review of the population PK analyses for the CML NDA and the current GIST NDA. The final estimate for the typical value of clearance in the prior NDA (70 kg CML patient of age 50) is 10.4 L and the typical value of clearance in the current NDA (GIST patient of any weight and age) is 8.48 L. Thus, our current best estimate is that AUC is GIST patients is approximately 20% higher in GIST patients than in CML patients. Consistent with our policy that, except in unusual circumstances, a 20% difference in AUC is negligible (bioequivalent), we recommend that the package insert be modified to include a statement that pharmacokinetics are

similar between CML and GIST patients (see section ***V. Detailed labeling recommendations*).**

The second intrinsic variable examined is ethnic origin. The current NDA includes a study in Japanese CML patients, the results of which are summarized in the Applicant's Table 3-4. which has been reproduced below (from NDA Item 6 p. 6-16).

**APPLICANT'S TABLE 3.4:**

**Table 3-4. Comparison of PK parameters at steady state between Japanese and non-Japanese CML patients**

| | 400 mg | | 600 mg | |
|---|---|---|---|---|
| | Japanese (n=3) | Non-Japanese (n=5) | Japanese (n=6) | Non-Japanese (n=9) |
| Cmax (ng/ml) | 2141±670 | 2595±787 | 3938±2524 | 3509±1649 |
| $T_{1/2}$ (h) | 18.0±4.9 | 19.3±4.4 | 18.2±3.4 | 15.6±5.0 |
| AUC (0-24) (µg.h/ml) | 33.2±14.9 | 40.1±15.7 | 66.1±40.8 | 51.7±26.7 |
| Vz/F (L) | 328.2±51.7 | 295.0±62.5 | 283.8±103.9 | 296.9±102.5 |
| Cl/F (L/h) | 13.6±5.4 | 11.2±4.0 | 11.2±4.8 | 14.4±6.8 |

Source: [1201] Tables 2 and 3 and original NDA [03 001] appendix 8.1.1.

Based upon these data the Applicant concludes that there are no remarkable pharmacokinetic differences between Japanese and non-Japanese CML patients. The FDA Reviewer agrees, but with a caveat. The analytical methods for this study are not included with the NDA, and the Reviewer can not complete review of the study until they are provided by the Applicant.

### *D. Extrinsic Factors*

*What extrinsic factors influence exposure and/or response and should this information be used to change the package insert?*

A single extrinsic factor was examined in the current NDA. The final results of a study of the effect of imatinib on simvastatin pharmacokinetics. A review of this final study report study is included in Appendix B. The preliminary results of this study have been previously reviewed and resulted in the following sections in the package insert:

**CLINICAL PHARMACOLOGY, Drug-Drug Interactions**

***CYP3A4 Substrates:*** Imatinib increased the mean $C_{max}$ and AUC of simvastatin (CYP3A4 substrate) by 2- and 3.5- fold, respectively, indicating an inhibition of CYP3A4 by imatinib. (See PRECAUTIONS.)

**PRECAUTIONS, Drug Interactions**

***Drugs that may have their plasma concentration altered by Gleevec***

Imatinib increases the mean $C_{max}$ and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5- fold, respectively, suggesting an inhibition of the CYP3A4 by imatinib.

The current results (p. 6-17 of Item 6 of the current NDA) are reproduced below. These results are consistent with the current package insert and neither the Reviewer nor the Applicant has suggested that the current insert be revised based upon these new data.

**APPLICANT'S TABLE 3.5:**

**Table 3-6. Simvastatin PK parameters following oral administration of 40 mg Simvastatin alone and combined with oral administration of 400 mg Glivec®**

| | Simvastatin plus Glivec® | Simvastatin alone |
|---|---|---|
| $t_{max}$ (h)* | 1.0 [redacted] | 1.0 [redacted] |
| $C_{max}$ (ng/mL) | 42.3±25.8 | 23.3±23.8 |
| $t_{½}$ (h) | 2.7±1.3 | 1.4±0.8 |
| $AUC_{(0-all)}$ (ng.h/mL) | 136.4±113.6 | 45.5±61.1 |
| $AUC_{(0-\infty)}$ (ng.h/mL) | 137.7±110.2 | 47.2±60.4 |
| $V_z/F$ (L) | 1543.0±810.9 | 3115.9±2749.9 |
| CL/F (L/h) | 504.1±431.8 | 2000.3±1975.3 |

all unflagged values are mean ± SD

* = median (range)

### *E. General Biopharmaceutics*

*What are the biopharmaceutical attributes of the drug product?*

The current NDA is for a new indication for the currently marketed drug product and the currently marketed drug product was used in all studies. See the review of NDA 21-335 for CML – Appendix E. for the attributes of the drug product.

### *F. Analytical*

*What bioanalytical methods were used to support the Clinical Pharmacology and Biopharmaceutics studies and were these methods adequate?*

Analytical methods have been reviewed as part of the individual study reviews for the two studies reviewed (population PK study and simvastatin study). See Appendix C. and B., respectively for these reviews. The Reviewer identified no analytical methods problems with either study.

## *V. Detailed labeling recommendations*

The package insert should be modified to include a statement that pharmacokinetics are similar between CML and GIST patients.

## current package insert:

CLINICAL PHARMACOLOGY
Mechanism of Action
Pharmacokinetics

... At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and $\alpha_1$-acid glycoprotein.

Metabolism and Elimination

## new package insert:

CLINICAL PHARMACOLOGY
Mechanism of Action
Pharmacokinetics

... At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and $\alpha_1$-acid glycoprotein.

The pharmacokinetics of imatinib in CML and GIST patients are similar.

Metabolism and Elimination

## *VI. Appendix A. – Proposed Package Insert (Original and Annotated)*

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ON ORIGINAL

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

(pp.) 10 - 28

| Reference # | Reference | Section / Page |
|---|---|---|
| 1 | Tuveson DA, Willis NA, Jacks T, Griffin JD, Singer S, Fletcher CDM, Fletcher JA, Demetri GD. STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. Oncogene 2001;20:5054-5058. | Clinical Pharmacology/Page 2 |
| 2 | This was a typing error in which the untreated and pre-treated values were inadvertently switched in the original CML PI. | Refer to CML NDA 21-335, dated 2/27/01, Vol. 50, Pg 8-57 (aka page 44 of Study Report for P102) |
| 3 | Clinical Study Report for CSTI571B2222 | Section 7.4/page 34 |
| 4 | Lux, ML, Rubin, BP, Biase, TL, Chen, C-J, et al. KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. American Journal of Pathology 2000;156:791-795 | Clinical Studies/Page 6 |
| 5 | Clinical Study Report for CSTI571B2222 | Section 3.5.2/page 22 |
| 6 | Clinical Study Report for CSTI571B2222 | |
| 7 | Clinical Study Report for CSTI571B2222 | Section 9.1.1/Table 9-2 |
| 8 | Clinical Study Report for CSTI571B2222 | Section 9.1.2/page 43 |
| 9 | Integrated Summary of Benefits and Risks | Section 6, Discussion/page 34 |
| 10 | Clinical Study Report for CSTI571B2222 | Section 10.2.1/page 53 |
| 11 | Clinical Study Report for CSTI571B2222 | Section 10.2.1/Table 10-7 |
| 12 | Clinical Study Report for CSTI571B2222 | This table in the PI is constructed using the data in Section 10.1, Tables 10-2 and 10-3 |
| 13 | Clinical Study Report for CSTI571B2222 | This table in the PI is constructed using the data in Section 10.3, Tables 10-8 and 10-9 |
| 14 | Integrated Summary of Benefits and Risks | Section 6.2.1 / page 34 |
| 15 | Protocol No. CST1571B2222 "Open, Randomized, Phase II Study of STI571 in Patients with unresectable or metastatic malignant gastrointestinal Stromal Tumors Expressing c-kit". | Section 3.3.3 / page 12 |

## *VI. Appendix B. – Individual Study Reviews*

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**Title of study:** An open-label, non-randomized, one-sequence crossover study to investigate the effects of ST1571 on the pharmacokinetics of simvastatin in patients with chronic myeloid leukemia.

**Objectives:**
Primary objective -- To investigate the effect of the co-administration of STI571 on the pharmacokinetics of simvastatin.
Secondary objective -- To investigate the tolerability of STI571 alone or in combination with simvastatin.

**Design:** This was a two center, open-label, non-randomized, one-sequence, crossover design, study. Twenty patients with chronic myeloid leukemia were enrolled in this study. Patients who discontinued prematurely were replaced. Each patient received
40 mg of simvastatin on study day 1,
400 mg of 571 on days 2-7
400 mg ST1571 + 40 mg simvastatin on day 8.
There was no washout phase for STI571 between treatments.

This was an out-patient study. On study days 1 and 8, patients reported to the study site ca. 1 hour prior to dosing for baseline evaluations and were kept at the center until 12 hours post-dosing; 24 hours after dosing, the patients reported again to the study site for the 24 hour blood sampling (study days 2 and 8) and study completion evaluations (study day 9).

The labeled dose of simvastatin is 5 – 80 mg/day. At the 80 mg/day dose of simvastatin the regimen is 40 prior to bedtime and 20 mg twice during daytime hours. The product label indicates that simvastatin pharmacokinetics are linear up to a dose of 120 mg. The label does not indicate if this linearity assessment was made upon single or multiple dosing. Tmax and half-life of simvastatin, based upon the current study (Tmax and half-life do not appear in the product label), are 1.0 and 1.4 hours, respectively. Based upon this half-life, accumulation of simvastatin using the labeled regimen should be slight. Thus, the current dose of 40 mg is probably appropriate

The labeled dose for imatinib (STI571) is 400 – 600 mg QD and the accumulation ratio given in the label is 1.5- 2.5- fold. The label states that AUC is proportional to dose from 25 – 1000 mg. Although an imatinib dose of 600 mg would have made for a better study than the 400 mg dose chosen, the Reviewer judges that the current study design will allow for assessment of the effect of imatinib treatment on the pharmacokinetics of 40 mg simvastatin.

**Number of patients:** 20 patients entered and completed the study

**Criteria for inclusion:** Patients with Chronic Myeloid Leukemia who are Hematologically or Cytogenetically Resistant or Refractory to Interferon-Alpha or Intolerant of Interferon-Alpha.

**Investigational drug:** STI571, 100 mg hard gelatin capsule

| Country | Formulation No. | Batch No. |
|---|---|---|
| Germany | KN 3752425.00.002 | X023 0100 |
| UK | KN 3758877.00.002 | X023 0100 |

**Comparator drug:** Simvastatin (Denan@) 40mg tablets

| Medication | Batch No. |
|---|---|
| Germany | Ch-B.: 2018100 |
| UK | Ch-B.: 2018100 |

**Blood collection:** All blood samples were taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein at predose (0 h), 0.5, 1, 2, 3, 4, 6, 10, 12 and 24 h after dosing on days 1 and 8.

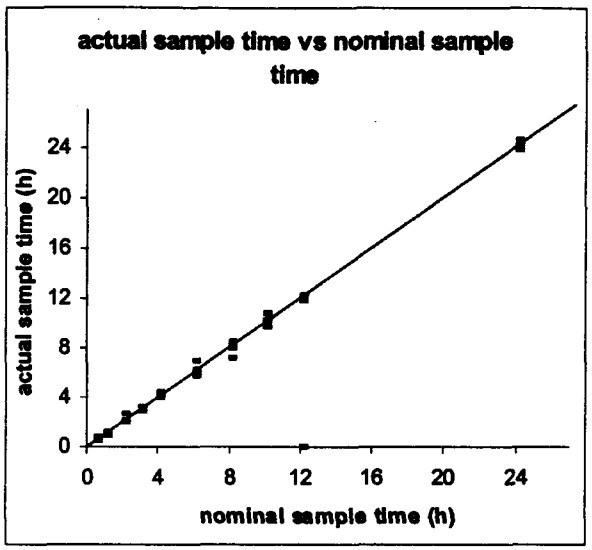
**Deviations from protocol and analytical methods concerns:**

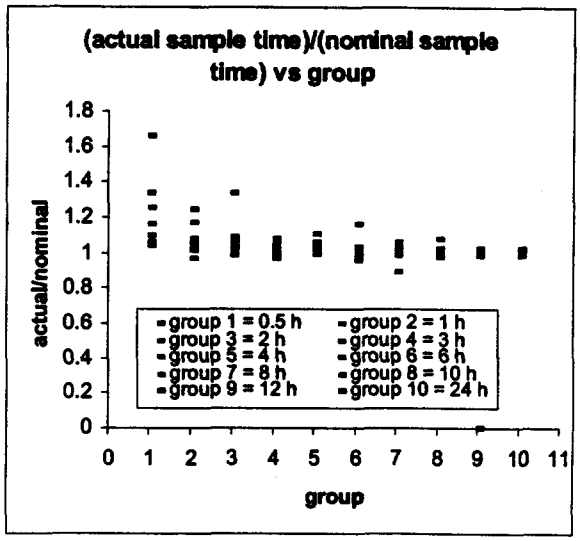
- The figures below shows how the actual sample times deviated from the planned sampling timepoints. The Reviewer judges that these deviations do not significantly compromise the study results.

| Figure 1.1 Sampling | | |
|---|---|---|
| | **total** | **% of total** |
| **samples** | 440 | 100.00 |
| **deviations from nominal time** | 168 | 38.18 |
| **not collected** | 2 | 0.45 |

| Figure 1.2 Summary Statistics of Sample Time Deviations | | |
|---|---|---|
| | **absolute value of sample time deviation (h)[1]** | **absolute value of % deviation in sample time[2]** |
| **mean** | 0.14 | 4.75 |
| **median** | 0.08 | 2.20 |
| **range** | | |

[1](actual sample time - nominal sample time)
[2](actual sample time - nominal sample time)/(nominal sample time) * 100




- One patient (#5102) took STI571 dose on day 8 before driving to the hospital for pre-dose sample; consequently the predose sample was re-scheduled.

- One patient (#10) took forbidden concomitant medication (oxazepam) on sampling day 8.

- A dilution and re-assay procedure for samples above the upper-limit-of-quantitation (ULOQ) is mentioned in the Bioanalytical Data Report, but details and validation of this procedure, and identifcation of which samples underwent this procedure, is not included in the Report. Upon query by the Reviewer, the Applicant has indicated that no samples were re-assayed due to exceeding ULOQ and that the Bioanalytical Report should not include the ULOQ re-assay statement (Robert Miranda, Novartis, personal communication).

**Assay**: A description of the assay method and in process validation begins on p. 6 of this review. The Reviewer judges that the assay is of sufficient quality to allow for review of the pharmacokinetic results. Please note bullet 4 in the **"Deviations from protocol and analytical methods concerns"** above.

**Pharmacokinetic Results:** The tables below (**7.4.3, 7.4.4, 7.4.1** and **7.4.2**) were excerpted from Volume 6 of the submission

**Table 7.4-3. Ratios of 'STI571+simvastatin'/'simvastatin' and corresponding 90%-confidence-intervals (%) for simvastatin (analyte)**

| Parameter | DF | Ratio | Confidence-Interval |
|---|---|---|---|
| $AUC_{all}$ | 19 | 370.6 | 272.0 – 504.9 |
| $AUC_{inf}$ | 19 | 325.5 | 159.8 – 478.4 |
| $C_{max}$ | 19 | 238.7 | 171.2 – 332.8 |
| Vz/f | 19 | 58.3 | 45.7 – 74.3 |
| Cl/f | 19 | 28.4 | 20.9 – 28.5 |
| $T_{1/2}$ [1)] | 19 | 1.3 | 0.79 – 1.80 |

1) Note : This is the (untransformed) difference between treatments

**Table 7.4-4. Ratios of 'STI571+simvastatin'/'simvastatin' and corresponding 90%-confidence-intervals (%) for simvastatin-hydroxyacid (analyte)**

| Parameter | DF | Ratio | Confidence-Interval |
|---|---|---|---|
| $AUC_{all}$ | 18 | 266.4 | 179.0 – 396.6 |
| $AUC_{inf}$ | 16 | 229.3 | 162.7 – 323.2 |
| $C_{max}$ | 18 | 168.2 | 130.4 – 217.0 |
| Vz/f | na. | na. | na. |
| Cl/f | na. | na. | na. |
| $T_{1/2}$ [1)] | 16 | 0.9 | 0.17 – 1.61 |

1) Note : This is the (untransformed) difference between treatments

**Table 7.4-1. Simvastatin PK parameters following oral administration of 40 mg simvastatin alone and combined with oral administration of 400 mg STI571**

| | Simvastatin plus STI571 | Simvastatin alone |
|---|---|---|
| $t_{max}$ (h) * | 1.0 | 1.0 |
| $C_{max}$ (ng/mL) | 42.3±25.8 | 23.3±23.8 |
| $t_{½}$ | 2.7±1.3 | 1.4±0.8 |
| $AUC_{(0\text{-}all)}$ (ng.h/mL) | 136.4±113.6 | 45.5±61.1 |
| $AUC_{(0\text{-}\infty)}$ (ng.h/mL) | 137.7±110.2 | 47.2±60.4 |
| $V_z$/F (L) | 1543.0±810.9 | 3115.9±2749.9 |
| CL/F (L/h) | 504.1±431.8 | 2000.3±1975.3 |

all unflagged values are mean ± SD

* = median (range)

**Table 7.4-2. PK parameters of simvastatin hydroxy acid following oral administration of 40 mg simvastatin alone and combined with oral administration of 400 mg STI571**

| | Simvastatin plus STI571 | Simvastatin alone |
|---|---|---|
| $t_{max}$ (h)* | 1.0 | 1.0 |
| $C_{max}$ (ng/mL) | 24.9±19.3 | 14.5±13.3 |
| $t_{½}$ | 3.3±1.4 | 2.4±1.1 |
| $AUC_{(0\text{-}all)}$ (ng.h/mL) | 116.1±104.2 | 44.3±41.7 |
| $AUC_{(0\text{-}\infty)}$ (ng.h/mL) | 119.9±106.0 | 51.9±39.9 |

all unflagged values are mean ± SD

* = median (range)

**Conclusions**

- Treatment with STI571 increases the AUC of simvastatin 3.7-fold and the Cmax of simvastatin 2.4-fold.

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pages of trade secret and/or confidential commercial information

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**Table 5.2-1: Daily variation of calibration parameters for Simvastatin**

| Analysis Run | Slope | y-Intercept | Correlation Coefficient (r) |
|---|---|---|---|
| 22-Dec-00 | | | |
| 24-Dec-00 | | | |
| 27-Dec-00 | | | |
| 27-Dec-00 | | | |
| 28-Dec-00 | | | |
| 02-Jan-01 | | | |
| 03-Jan-01 | | | |
| 07-Feb-01 | | | |
| 08-Feb-01 | | | |
| 16-Feb-01 | | | |
| 28-Feb-01 | | | |
| 11-Mar-01 | | | |
| Mean | 0.0271 | 0.0218 | 0.9962 |

**Table 5.2-2: Daily variation of calibration parameters for Simvastatin Hydroxy Acid**

| Analysis Run | Slope | y-Intercept | Correlation Coefficient (r) |
|---|---|---|---|
| 22-Dec-00 | | | |
| 24-Dec-00 | | | |
| 27-Dec-00 | | | |
| 27-Dec-00 | | | |
| 28-Dec-00 | | | |
| 02-Jan-01 | | | |
| 03-Jan-01 | | | |
| 07-Feb-01 | | | |
| 08-Feb-01 | | | |
| 16-Feb-01 | | | |
| 28-Feb-01 | | | |
| 11-Mar-01 | | | |
| Mean | 1915 | 1875 | 0.9933 |

**Table 5.2-3: Daily variation of calibration parameters for STI571**

| Analysis Run | Slope | y-Intercept | Correlation Coefficient (r) |
|---|---|---|---|
| 08-Jan-01 | | | |
| 01-Mar-01 | | | |
| Mean | 0.0120 | -0.01449 | 0.9925 |

**Table 5.2-4: Daily variation of calibration parameters for CGP74588**

| Analysis Run | Slope | y-Intercept | Correlation Coefficient (r) |
|---|---|---|---|
| 08-Jan-01 | | | |
| 01-Mar-01 | | | |
| Mean | 0.00848 | -0.0154 | 0.9891 |

## 5.4. C Sample Results

**Table 5.3-1: Accuracy and precision of Simvastatin C samples**

| Analysis Day | Concentration ng/mL | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 5 | 10 | 100 | 250 | 500 |
| 22-Dec-00 | | | | | | |
| 24-Dec-00 | | | | | | |
| 27-Dec-00 | | | | | | |
| 27-Dec-00 | | | | | | |
| 28-Dec-00 | | | | | | |
| 02-Jan-01 | | | | | | |
| 03-Jan-01 | | | | | | |
| 07-Feb-01 | | | | | | |
| 08-Feb-01 | | | | | | |
| 16-Feb-01 | | | | | | |
| 28-Feb-01 | | | | | | |
| 11-Mar-01 | | | | | | |
| Mean | 0.993 | 5.15 | 10.1 | 101 | 247 | 493 |
| SD | 0.0789 | 0.446 | 0.833 | 9.60 | 22.6 | 41.7 |
| CV % | 7.95 | 8.65 | 8.21 | 9.52 | 9.15 | 8.47 |
| % Recovery | 99.3 | 103 | 101 | 101 | 98.8 | 98.5 |

[a]: C sample didn't meet the acceptance criteria and was excluded from the calculation.

NR: No Results

NA: C sample not analyzed

**Table 5.3-2: Accuracy and precision of Simvastatin Hydroxy Acid C samples**

| Analysis Day | Concentration ng/mL 1 | 5 | 10 | 100 | 250 | 500 |
|---|---|---|---|---|---|---|
| 22-Dec-00 | | | | | | |
| 24-Dec-00 | | | | | | |
| 27-Dec-00 | | | | | | |
| 27-Dec-00 | | | | | | |
| 28-Dec-00 | | | | | | |
| 02-Jan-01 | | | | | | |
| 03-Jan-01 | | | | | | |
| 07-Feb-01 | | | | | | |
| 08-Feb-01 | | | | | | |
| 16-Feb-01 | | | | | | |
| 28-Feb-01 | | | | | | |
| 11-Mar-01 | | | | | | |
| Mean | 0.999 | 4.94 | 10.4 | 102 | 249 | 489 |
| SD | 0.0703 | 0.440 | 1.10 | 11.0 | 21.9 | 49.7 |
| CV % | 7.04 | 8.92 | 10.6 | 10.8 | 8.76 | 10.2 |
| % Recovery | 99.9 | 98.7 | 104 | 102 | 99.8 | 97.8 |

[a]: C sample didn't meet the acceptance criteria and was excluded from the calculation.

NR: No Results

NA: C sample not analyzed

**Table 5.3-3: Accuracy and precision of STI571 C samples**

| Analysis Day | Concentration ng/mL 4 | 10 | 20 | 100 | 1000 | 10000 |
|---|---|---|---|---|---|---|
| 08-Jan-01 | | | | | | |
| 01-Mar-01 | | | | | | |
| Mean | 4.30 | 8.60 | 18.1 | 100 | 1100 | 10800 |
| SD | 0.090 | 0.176 | 0.698 | 5.72 | 33.0 | 100 |
| CV % | 2.10 | 2.04 | 3.85 | 5.69 | 3.01 | 0.926 |
| % Recovery | 107 | 86.0 | 90.5 | 100 | 110 | 108 |

[a]: C sample didn't meet the acceptance criteria and was excluded from the calculation.

**Table 5.3-4: Accuracy and precision of CGP74588 C samples**

| Analysis Day | Concentration ng/mL 4 | 10 | 20 | 100 | 1000 | 10000 |
|---|---|---|---|---|---|---|
| 08-Jan-01 | | | | | | |
| 01-Mar-01 | | | | | | |
| Mean | 4.24 | 8.80 | 17.9 | 90.6 | 1120 | 11500 |
| SD | 0.235 | 0.478 | 1.47 | 6.39 | 29.4 | 252 |
| CV % | 5.54 | 5.43 | 8.22 | 7.06 | 2.63 | 2.19 |
| % Recovery | 106 | 88.0 | 89.5 | 90.6 | 112 | 115 |

[a]: C sample didn't meet the acceptance criteria and was excluded from the calculation

**Table 5.4-1: Accuracy and precision of Simvastatin QC samples**

Accuracy expressed as percent recovery.

| Analysis Day | Concentration ng/mL 1 | 5 | 100 | 500 |
|---|---|---|---|---|
| | Accuracy (%) | | | |
| 22-Dec-00 | | | | |
| 24-Dec-00 | | | | |
| 27-Dec-00 | | | | |
| 27-Dec-00 | | | | |

| Analysis Day | Concentration ng/mL 1 | 5 | 100 | 500 |
|---|---|---|---|---|
| 28-Dec-00 | | | | |
| 02-Jan-01 | | | | |
| 03-Jan-01 | | | | |
| 07-Feb-01 | | | | |
| 08-Feb-01 | | | | |
| 16-Feb-01 | | | | |
| 28-Feb-01 | | | | |
| 11-Mar-01 | | | | |
| Mean | 96.4 | 101 | 99.5 | 95.2 |
| SD | 11.7 | 7.24 | 5.85 | 6.50 |
| CV % | 12.2 | 7.20 | 5.87 | 6.82 |

[a]: QC sample didn't meet the acceptance criteria and was excluded from the calculation.

**Table 5.4-2: Accuracy and precision of Simvastatin Hydroxy Acid QC samples**

Accuracy expressed as percent recovery.

| Analysis Day | Concentration ng/mL 1 | 5 | 100 | 500 |
|---|---|---|---|---|
| | Accuracy (%) | | | |
| 22-Dec-00 | | | | |
| 24-Dec-00 | | | | |
| 27-Dec-00 | | | | |
| 27-Dec-00 | | | | |
| 28-Dec-00 | | | | |
| 02-Jan-01 | | | | |
| 03-Jan-01 | | | | |
| 07-Feb-01 | | | | |
| 08-Feb-01 | | | | |
| 16-Feb-01 | | | | |

| Analysis Day | Concentration ng/mL 1 | 5 | 100 | 500 |
|---|---|---|---|---|
| 28-Feb-01 | | | | |
| 11-Mar-01 | | | | |
| Mean | 98.1 | 103 | 101 | 101 |
| SD | 9.44 | 6.14 | 7.67 | 7.41 |
| CV % | 9.62 | 5.92 | 7.54 | 7.34 |

[a]: QC sample didn't meet the acceptance criteria and was excluded from the calculation

**Table 5.4-3: Accuracy and precision of STI571 QC samples**

Accuracy expressed as percent recovery.

| Analysis Day | Concentration ng/mL 4 | 10 | 1000 | 10000 |
|---|---|---|---|---|
| | Accuracy (%) | | | |
| 08-Jan-01 | | | | |
| 01-Mar-01 | | | | |
| Mean | 100 | 103 | 110 | 105 |
| SD | 18.7 | 14.7 | 2.08 | 2.50 |
| CV % | 18.7 | 14.3 | 1.90 | 2.39 |

[a]: QC sample didn't meet the acceptance criteria and was excluded from the calculation

**Table 5.4-4: Accuracy and precision of CGP74588 QC samples**

Accuracy expressed as percent recovery.

| Analysis Day | Concentration ng/mL 4 | 10 | 1000 | 10000 |
|---|---|---|---|---|
| | Accuracy (%) | | | |
| 08-Jan-01 | | | | |
| 01-Mar-01 | | | | |
| Mean | 94.9 | 102 | 111 | 112 |
| SD | 18.4 | 6.61 | 3.51 | 1.15 |
| CV % | 19.4 | 6.46 | 3.15 | 1.03 |

[a]: QC sample didn't meet the acceptance criteria and was excluded from the calculation

## *VI. Appendix C. – Pharmacometric Review: Review of Population PK Analysis*

## Review of the Population Pharmacokinetics Analysis of NDA 21335

## I. Study Synopsis

**Study design**: This is a randomized, open label, two-arm, multi-center, phase II clinical trial testing of Gleevec in a population of patients with unresectable or metastatic malignant GIST.

**Dose groups**: 400 and 600 mg

**No. of subjects**: Seventy-three patients contributed plasma samples.

**Sampling schedule**: Full profile pharmacokinetic samples were obtained for 10 patients at the 400 mg dose and 9 patients at the 600 mg dose. On Day 1, samples were taken at pre-dose, 1, 2, 3, 8, 24, 48, and 72 hrs. On Day 29 samples were taken at pre-dose, 1, 2, 3, 8, and 24 h (prior to resuming study drug). Sparse sampling was conducted on days 1 and 29 at three times: 1-3 h, 6-9 h and 24 h.

**Analytical Methods:** The analytical methods review is at the end of the review portion of this document (p. 7). The Reviewer judges that the assay is of sufficient quality to allow for review of the pharmacokinetic results.

### II. Applicant's Analysis

The Applicant's Summary of the Population Pharmacokinetics analysis is included as an Appendix to this review (Appendix 2. – p.16 of this document).

The Applicant's analysis followed a 5-step process which is summarized in Figure 1. below.

| Figure 1. Summary of Applicant's Model Building Process | | |
|---|---|---|
| modeling stage | models investigated | model selected |
| 1. selection of a structural (pharmacokinetic) model | 1-cpt: 1st-order input and output | 1-cpt: 0-order input and 1st-order output |
| | 1-cpt: input lag, 1st-order input and output | |
| | 1-cpt: 0-order input and 1st-order output | |
| | 2-cpt: 0-order input and 1st-order output | |
| 2. selection of a residual error model | proportional | proportional + additive |
| | additive | |
| | proportional + additive | |
| 3. selection of an inter-subject random effects (OMEGA) model | OMEGA on ABS, V, Cl | BLOCK OMEGA on CL and V |
| | BLOCK OMEGA | |
| 4. 1-at-a-time forward selection of the covariate effects model | age, gender, weight, daily dose, creatnine, total WBC count, SGOT, SGPT, albumin, bilirubin, hemoglobin, presence of liver metastases, and edema | albumin on V, albumin on CL, bilirubin on V, WBC on CL |
| 5. 1-at-a-time backward elimination of the covariate effects model | albumin on V, albumin on CL, bilirubin on V, WBC on CL | none deleted, thus: albumin on V, albumin on CL, bilirubin on V, WBC on CL |

The parameter estimates for the final model, and the Applicant's interpretation, is available in Appendix 2 (p. x of this document).

The "conclusions" portion of the Applicant's section "**3. Summary and conclusions**" is reproduced below as Figure 2.

*Figure 2. Excerpt from Applicant's Summary and Conclusions*

**Pharmacokinetics of STI571 and influence of demographic characteristics**

- The remaining intersubject variability for apparent clearance dropped from 50.1 % to 40.7 % after accounting for covariates. The corresponding figures for apparent volume were 47.2 % and 38.7 %, respectively.
- Albumin, bilirubin and WBC at baseline were the only variables in explaining intersubject variability.
- Albumin affected apparent clearance of the drug more than linearly. E.g. doubling of albumin leads to an increase of *Cl/f*, which is more than doubled. It is noted that the superlinearity of this effect was mainly caused by two subjects whose apparent clearance were estimated as about 25 [L/h]. Excluding the data of these subjects shifted the effect of albumin towards linearity.
- Although the relationship between albumin and *Cl/f* is statistically significant and suggests that *Cl/f* increases by a factor of at least two over the range of albumin values, its utility as a predictor of exposure, particularly in patients whose levels of albumin are significantly below the lower normal range (34 g/L), is questionable. Scrutiny of the predicted *Cl/f* in this group revealed that about half the patients had values in the normal range despite subnormal albumin. Thus, using albumin to predict exposure in patients with subnormal albumin runs the risk of underexposing a significant proportion of this patient subpopulation.
- Remaining covariates, i.e., age, weight, gender, (serum) creatinine, SGOT, SGPT, hemoglobin, presence of liver metastases or edema did not affect the (serum) pharmacokinetic behavior of STI571.

- The model used considered the pharmacokinetic parameters *Cl/f* , *V/f* and $T_0$ to be constant with time. The analysis of residuals in Chapter 6.3 suggested that the model could be refined, if the parametrization would allow to take potential changes in pharmacokinetics over time into account.

## III. Reviewer's Analysis

Data was checked by creating a plot of each covariate versus patient ID. No values appeared unusual.

The Reviewer accepts the first 3-steps of Applicant's model building process: 1.selection of a structural (pharmacokinetic) model, 2. selection of a residual error model, and 3. selection of an inter-subject random effects (OMEGA) model. However, the Reviewer believes that selection of a covariate effects model should proceed slightly differently. the Reviewer is dividing the covariates into 2-categories: primary and secondary. Primary covariates are weight, age ($\geq$ 65 or < 65, continuous) and gender. Secondary covariates are all remaining covariates (daily dose, creatnine, total WBC count, SGOT, SGPT, albumin, bilirubin, hemoglobin, presence of liver metastases, and edema). The reason for dividing the covariates is mechanistic and pragmatic. Mechanistically, the Reviewer's expectation (based upon clinical pharmacology principles and the current labeling of Gleevec) is that the primary covariates will account for inter-individual variability. Pragmatically, the primary covariates do not necessitate clinical chemistry evaluation and interpretation, and thus are easier to use for making dose adjustments.

Primary covariates will be tested first (1-at-a-time forward selection) and retained in the model if they lower objective function by 6.63 or more ($p<0.01$). Once the set of significant primary covariates is identified, they will be retained in the model and the secondary covariates will be tested in the model one-at-a-time. Once a full model is identified, 1-at-a-time backward elimination of any secondary covariates will be performed to arrive at the final model (identical to the selection procedure used by the Applicant in step 5. of Figure 1. on p. 2 above).

## IV. Reviewer's Results

The initial model tested by the Reviewer (Applicant's structural, residual and OMEGA model) produced the identical result as that obtained by the Applicant. A reproduction of the NONMEM control file that produced this result is included at the end of this document (Appendix 1. – p. 12 of this document). Testing of the FDA primary covariates showed none to be significant (see Figure 3. on the next page). This result makes the remainder of the Reviewer's planned covariate selection procedure effectively identical to the Applicant's procedure, and was not repeated by the Reviewer. Testing of the Applicant's final model was performed by the Reviewer and resulted in estimates identical to those of the Applicant. A reproduction of the NONMEM control file that produced this result is included at the end of this document (Appendix 1. – p. 14 of this document). Based on these results the Reviewer assumed that backward elimination of the identified covariates would produce the same result as reported by the Applicant and the Reviewer discontinued analysis with the conclusion that he agrees with the Applicant's analysis. The Reviewer's final model (effectively identical to the Applicant's final model) is described in Figure 4 on the next page.

| *A. Figure 3. FDA Reviewer's NONMEM Model Building Results* | | |
|---|---|---|
| **Model** | **Objective Function value** | **Comments** |
| Base = 1-CPT, 0-order input, 1st-order output, BLOCK OMEGA on CL and V | 371.434 | identical to Applicant's result |
| Base + WT on V | 370.427 | |
| Base + AGE (continuous) on V | 368.222 | |
| Base + AGE (> or ≤ 65) on V | 367.819 | |
| Base + SEX on V | 371.398 | |
| Base + WT on CL | 371.433 | |
| Base + AGE (continuous) on CL | 368.099 | |
| Base + AGE (> or < 65) on CL | 371.43 | |
| Base + SEX on CL | 367.976 | |
| Base + albumin on V, albumin on CL, bilbirubin on V, WBC on CL | 332.275 | identical to Applicant's result |

| **Figure 4. FDA Reviewer's NONMEM Final Model** | | | | |
|---|---|---|---|---|
| **Minimization successful**<br>Number of significant digits in final estimate = 3.3 | | | | |
| **Parameter** | | **Estimate** | **Std Error of Estimate** | **Unit** |
| **description** | **NONMEM code** | | | |
| ABS Rate (0-order) | THETA(1) | 1.7 | 0.139 | h |
| V/F | THETA(2) | 186 | 9.78 | L |
| CL/F | THETA(5) | 8.48 | 0.487 | L/h |
| | | | | |
| random effect for V/F | ETA1 ETA1 | 0.15 | 0.0334 | |
| interaction between random effects for V/F and CL/F | ETA1 ETA2 | 0.138 | 0.0331 | |
| random effect for CL/F | ETA2 ETA2 | 0.166 | 0.0341 | |
| | | | | |
| albumin on V | THETA(3) | 1.55 | 0.393 | |
| albumin on CL | THETA(7) | 1.29 | 0.383 | |
| bilirubin on V | THETA(4) | -0.211 | 0.0535 | |
| WBC on CL | THETA(6) | -0.284 | 0.0758 | |
| | | | | |
| residual proportional | THETA(8) | 0.391 | 0.0206 | |
| residual additive | THETA(9) | 0.004 | 0.000167 | mg/L |

## V. Reviewer's Summary

The Reviewer's analysis confirms the Applicant's analysis: the final model includes the covariates albumin at study entry (reduces inter-individual variability in clearance and volume), bilirubin at study entry (reduces inter-individual variability in volume) and total white blood cell count at study entry (reduces inter-individual variability in clearance).

The effect of the covariates, relative to the total inter-individual variability in the parameters, is not pronounced: %CV of clearance is reduced from 50% to 41% and %CV of volume is reduced from 47 to 39%.

## VI. Reviewer's Interpretation and Conclusions

Four covariates were identified as statistically significant (albumin on V, albumin on CL, bilirubin on V, WBC on CL). The Reviewer has no mechanistic explanation for these effects. Further, the effect of albumin on V is in the opposite direction from the Reviewer's expectation: for a highly protein bound drug (Gleevec is 95% protein bound), the Reviewer has an expectation that V may decrease with increasing albumin. The mechanism underlying this expectation is that as albumin increases protein binding increases resulting in less drug escaping the plasma compartment and a smaller V. However, the Gleevec model shows the opposite relationship: V increased as albumin increased.

Consistent with the Reviewer, the Applicant offers no mechanistic explanation for the statistically significant covariates. This lack of mechanistic support increases a typical concern for population pharmacokinetic analyses: significance of the covariate effects may have resulted from chance (multiplicity of covariates tested resulting in false positives) rather than a true effect.

As forementioned (**V. Reviewer's Summary**), the effect of the covariates, relative to the total inter-individual variability in the parameters, is not pronounced: incorporation of the covariates reduces %CV of clearance from 50% to 41% and %CV of volume from 47 to 39%.

Based on

- the lack of mechanistic underpinning,
- the relative ineffectiveness of the covariates in accounting for inter-individual variability,
- and the current lack of a known relationship between Gleevec concentration and effectiveness and safety,

the Reviewer concludes that the current analysis does not indicate that dose should be modified as a function of albumin, bilirubin or white blood cell count. This agrees with the conclusions of the Applicant: the Applicant has not suggested dose modification based upon the identified covariates. No labeling changes have been recommended by the Applicant and none are recommended by the Reviewer.

**Analytical method**: ST1571 (parent Gleevec) with D8-STI571 as internal standard were determined in plasma by [redacted]

- Sample Preparation
  Samples were prepared using protein precipitation. Plasma (250 uL) was spiked with 25 ng of internal standard in 50uL, and 250uL of acetonitrile. Samples were centrifuged and analyzed by [redacted]

- Instrumental Conditions
  [redacted] room temperature, isocratic elution, ammonium acetate (0.05%) in water:methanol (28:72, v/v), flow-rate of 1 mL/min., inj volume 10 uL.
  Mass Spectrometer: [redacted] vaporizer temperature 450'C, corona discharge 5 uA, selected reaction monitoring, positive ion mode, collision energy -35 eV, mass resolution 0.7 amu, scan time 0.6 s for analyte and 0.1 s for internal standard.
  Masses STI571: Parent m/z 494, daughter m/z 394 (free base)
  Masses Internal Standard: Parent m/z 502, daughter m/z 394 (free base)

- Calibration Curves
  Calibration model $y = a + b*x$, $1/x^2$ weighting
  y Peak area ratio of reference compound to internal standard
  x Concentration of reference compound in C samples
  Criteria for LLOQ : Mean accuracy of C samples within 80% - 120%, CV $\leq$ 20%

- Performance
  Salient features of the performance of the analytical methods are documented in the Applicant's Tables 5.2-1, 5.2-2 and 5.3-1 which are reproduced below.

*Overall LLOQ* STI571: g/mL
CGP 74588: ng/mL

*Deviations from overall LLOQ* None

**Table 5.2-1: Daily variation of calibration parameters**

**STI571**

| Analysis Date | Weighted Regression Analysis | | |
|---|---|---|---|
| | Slope (b) | y-intercept (a) | Correlation Coefficient (r) |
| 15-Aug-00 | | | |
| 30-Aug-00 | | | |
| 27-Oct-00 | | | |
| 28-Oct-00 | | | |
| 09-Nov-00 | | | |
| 29-Nov-00 | | | |
| 01-Mar-01 | | | |
| 10-Apr-01 | | | |
| 01-May-01 | | | |
| | | | |
| Mean | 0.0107 | | 0.9933 |
| SD | 0.0007 | | 0.0018 |
| CV% | 6.87 | | 0.1860 |

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**Table 5.2-2.: Individual and mean accuracy (% recovery) of C samples in plasma**

**STI571**

| Run | Analysis Date | Added concentration (ng/mL) 4 | 8 | 10 | 20 | 100 | 1000 | 5000 | 10000 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 15-Aug-00 | | | | | | | | |
| 2 | 30-Aug-00 | | | | | | | | |
| 3 | 10/27/2000** | | | | | | | | |
| 4 | 28-Oct-00 | | | | | | | | |
| 5 | 9-Nov-00 | | | | | | | | --- |
| 6 | 29-Nov-00 | * | | | | | | | |
| 7 | 1-Mar-01 | | | | | | | | |
| 8 | 10-Apr-01 | | | | | | | | |
| 9 | 1-May-01 | | | | | | | | |
| | | 1 | | | | | | | |
| Mean | | 106 | 93.5 | 92.6 | 93.2 | 93.5 | 107 | 97.6 | 103 |
| CV (%) | | 7.93 | 5.53 | 8.79 | 8.74 | 9.73 | 5.88 | 10.06 | 5.02 |

* = Not used in calculations

** = LLOQ for this run is 'mL.

## 5.3. QC Sample Results

**Table 5.3-1: Accuracy and precision of STI571 QC samples**

| | Concentration added (ng/mL) | | | | |
|---|---|---|---|---|---|
| | 4 | 8 | 200 | 4200 | 8400 |
| Analysis date | Recovery % | | | | |
| 15-Aug-00 | | | | | |
| 30-Aug-00 | | | | | |
| Mean | 95.4 | 112 | 102.4 | 98.8 | 97.9 |
| SD | 8.81 | 1.00 | 4.16 | 3.91 | 2.91 |
| CV(%) | 9.23 | 0.893 | 4.06 | 3.96 | 2.97 |

| | Concentration added (ng/mL) | | | |
|---|---|---|---|---|
| | 4 | 10 | 1000 | 10000 |
| Analysis date | Recovery % | | | |
| 10/27/2000** | | | | |
| 28-Oct-00 | | | | |
| 9-Nov-00 | | | | |
| 29-Nov-00 | | | | |
| 1-Mar-01 | | | | |
| 10-Apr-01 | | | | |
| 1-May-01 | | | | |
| Mean | 100 | 99.5 | 105 | 105 |
| SD | 14.1 | 9.72 | 7.56 | 5.76 |
| CV(%) | 14.1 | 9.77 | 7.22 | 5.50 |

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**Appendix 1. NONMEM control files for FDA's base and final models**

**FDA base model**

```
$PROBLEM STI POPULATION PK USING DATA FROM STI571B-2222
$INPUT ID TIME AMT DV MDV EVID SS II RATE SEX AGE WT WBC
               SGPT SGOT CREA ALB HGB BIL LC
$DATA  applicant.dat LRECL=101 IGNORE=C
$SUBROUTINES ADVAN1 TRANS2 DOUBLE
$PK

     IF (AMT .NE. 0) C1 = AMT/400.0
                     C2 = 0.0            ;  males
     IF (SEX .EQ. 2) C2 = 1.0            ;  females
                     C3 = 0.0            ;  age < 65
    IF (AGE .GE. 65) C3 = 1.0            ;  age >= 65
                     C4 = WT/75.0
                     C5 = WBC/7.0
                     C6 = SGPT/27.0
                     C7 = SGOT/27.0
                     C8 = CREA/80.0
                     C9 = ALB/38.0
                    C10 = HGB/122.0
                    C11 = BIL/10.0
                    C12 = 0.0            ;  no liver tumor
     IF (LC .EQ. 1) C12 = 1.0            ;  liver tumor
                    C13 = 0.0            ;  edema at baseline
IF (ID .EQ. 19 .OR. ID .EQ. 47 .OR. ID .EQ. 51 .OR. ID .EQ. 56)  C13 = 1.0
IF (ID .EQ. 68 .OR. ID .EQ. 41 .OR. ID .EQ. 48 .OR. ID .EQ. 59)  C13 = 1.0
IF (ID .EQ. 61) C13 = 1.0

        D1 = THETA(1)
         V = THETA(2)*EXP(ETA(1))
        CL = THETA(3)*EXP(ETA(2))

        S1 = V

$ERROR

         A = F**2.0*THETA(4)**2.0 + THETA(5)**2.0
         Y = F + SQRT(A)*EPS(1)
     IPRED = F
      IRES = DV - IPRED

$THETA      (      0.1,        1.7       )  ;  THETA1  D1
            (    1.0  ,    170.0         )  ;  THETA2  V
            (      0.1,      8.0         )  ;  THETA3  CL
            (      0.0,        0.4       )  ;  *EPS
            (      0.0,        0.4       )  ;  +EPS

$OMEGA BLOCK (2) 0.3
                 0.1  0.3

$SIGMA  1.0  FIXED

$ESTIMATION METHOD=1 INTERACTION ABORT POSTHOC MAXEVAL=9999 PRINT=5
$COV
$TABLE NOPRINT ONEHEADER ID TIME SEX AGE WT WBC SGPT SGOT CREA ALB HGB BIL LC
```

```
ETA1 ETA2 IPRED IRES
FILE=m1.tbl
```

## FDA final model

```
$PROBLEM STI POPULATION PK USING DATA FROM STI571B-2222
$INPUT ID TIME AMT DV MDV EVID SS II RATE SEX AGE WT WBC
               SGPT SGOT CREA ALB HGB BIL LC
$DATA  applicant.dat LRECL=101 IGNORE=C
$SUBROUTINES ADVAN1 TRANS2 DOUBLE
$PK

     IF (AMT .NE. 0) C1 = AMT/400.0
                     C2 = 0.0            ;  males
     IF (SEX .EQ. 2) C2 = 1.0            ;  females
                     C3 = 0.0            ;  age < 65
    IF (AGE .GE. 65) C3 = 1.0            ;  age >= 65
                     C4 = WT/75.0
                     C5 = WBC/7.0
                     C6 = SGPT/27.0
                     C7 = SGOT/27.0
                     C8 = CREA/80.0
                     C9 = ALB/38.0
                    C10 = HGB/122.0
                    C11 = BIL/10.0
                    C12 = 0.0            ;  no liver tumor
     IF (LC .EQ. 1) C12 = 1.0            ;  liver tumor
                    C13 = 0.0            ;  edema at baseline
IF (ID .EQ. 19 .OR. ID .EQ. 47 .OR. ID .EQ. 51 .OR. ID .EQ. 56)  C13 = 1.0
IF (ID .EQ. 68 .OR. ID .EQ. 41 .OR. ID .EQ. 48 .OR. ID .EQ. 59)  C13 = 1.0
IF (ID .EQ. 61) C13 = 1.0

       D1 = THETA(1)
      TVV = THETA(2)*C9**THETA(3)*C11**THETA(4)
        V = TVV*EXP(ETA(1))
     TVCL = THETA(5)*C5**THETA(6)*C9**THETA(7)
       CL = TVCL*EXP(ETA(2))

       S1 = V

$ERROR

        A = F**2.0*THETA(8)**2.0 + THETA(9)**2.0
        Y = F + SQRT(A)*EPS(1)
    IPRED = F
     IRES = DV - IPRED

$THETA      (      0.1,       1.7      )  ;  D1
            (    1.0  ,   170.0         )  ;  V
            (-INFINITY,     0.7         )  ;  ALB on V
            (-INFINITY,    -0.2         )  ;  BIL on V
            (      0.1,     8.0         )  ;  CL
            (-INFINITY,    -0.5         )  ;  WBC on CL
            (-INFINITY,   1.2           )  ;  ALB on CL
            (      0.0,       0.4       )  ;  *EPS
            (      0.0,       0.4       )  ;  +EPS

$OMEGA BLOCK (2) 0.3
                 0.1  0.3
```

```
$SIGMA  1.0  FIXED

$ESTIMATION METHOD=1 INTERACTION ABORT POSTHOC MAXEVAL=9999 PRINT=5
$COV
$TABLE NOPRINT ONEHEADER ID TIME SEX AGE WT WBC SGPT SGOT CREA ALB HGB BIL LC
                         ETA1 ETA2 IPRED IRES
                         FILE=final.tbl
```

**Appendix 2. Applicant's Biostatistical Report: Population Pharmacokinetic Analysis**

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pages of trade

secret and/or

confidential

commercial

information

pp. 65-92

# *PHARMACOMETRICS REVIEW*

| | |
|---|---|
| **NDA:** | 21-335 |
| **SUBMISSION DATES:** | October 15, 2001 |
| **TYPE:** | S-01 |
| **BRAND NAME:** | Gleevec® Capsules |
| **GENERIC NAME:** | Imatinib Mesylate |
| **DOSAGE STRENGTH:** | 400 mg and 600 mg Capsules |
| **SPONSOR:** | Novartis Pharmaceuticals Corporation |
| **PRIMARY REVIEWER:** | Gabriel J. Robbie, Ph.D. |
| **TEAM LEADER:** | Joga Gobburu, Ph.D. |

## BACKGROUND

Gleevec was previously approved for use in the treatment of patients with chronic myeloid leukemia (CML) because of its selective inhibition of proliferation and induction of apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive CML and acute lymphoid leukemia (ALL) patients.

The sponsor is presently seeking approval of Gleevec for the treatment of patients with unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

## OBJECTIVES

1. To compare the pharmacokinetics of Gleevec in GIST and CML patients.
2. Evaluate the influence of patient covariates, age, body weight, WBC, SGOT, SGPT, hemoglobin, albumin and bilirubin on the pharmacokinetics of Gleevec in patients with GIST.

## METHODS

### STUDY CST1B 2222:

This was a randomized, open-label multinational study was conducted in 147 patients with unresectable or metastatic malignant GIST to support efficacy. Patients were randomized to receive Gleevec either 400 mg (n=73) or 600 mg (n=74) QD orally for up to 24 months. Pharmacokinetic data was obtained in 73 patients in Study CST1B 2222. Two profiles were obtained - one on Day 1 and a second one on Day 29. A full pharmacokinetic profile was obtained in 18 patients on Days 1 and 29 at 0, 1, 2, 3, 8 and 24 and at 48 and 72 hours post dose on Day 1. In the remaining patients sparse samples

were collected on Days 1 and 29 between 1 and 3 hours after drug intake, between 6 and 9 h after drug intake and before taking capsule on the following day.

Data from 7 patients were excluded from population analysis because of protocol deviations or due to vomiting.

## *Is the pharmacokinetics of Gleevec similar in GIST and CML patients?*

Yes, the pharmacokinetics of Gleevec is similar in GIST and CML patients.

### Absorption:

The sponsor evaluated the following 4 PK models to describe the PK of Gleevec.

a. 1-compartment model with Ist order input and output
b. 1-compartment model with Ist order input and output with a time lagged onset of action
c. 1-compartment model with zero order input and Ist order output
d. 2-compartment model with zero-order absorption

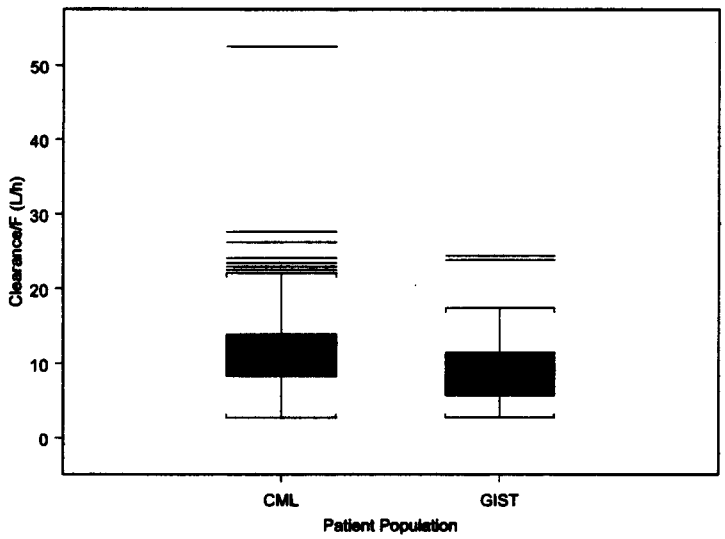
Based on the lowest mean AIC-value the sponsor chose 1-compartment model with zero-order absorption. The zero order absorption obtained in the present analysis which is probably a result of sparse sampling is contrasted with population PK analysis of Gleevec in CML patients (Original NDA) where Ist order absorption with a Ka of 1.05 $h^{-1}$ with larger interindividual variability of 75% was obtained. Modeling Gleevec absorption to a zero order process is more for methodological purposes and is not expected to occur physiologically.

**Elimination:**

The CL/F values in patients with GIST and CML were comparable. The typical value of CL/F obtained by the sponsor in patients with GIST was 8.48 L/h for an individual with baseline albumin concentration of 38 g/L and baseline WBC concentration of $7x10^9$/L (see Appendix I). The typical value for CL/F obtained by the reviewer is 8.07 L/h in GIST (see Appendix II). These values are comparable to the typical CL value of 10.4 L/h/70 kg/50 yr obtained in CML patients in the original NDA (see Appendix III).

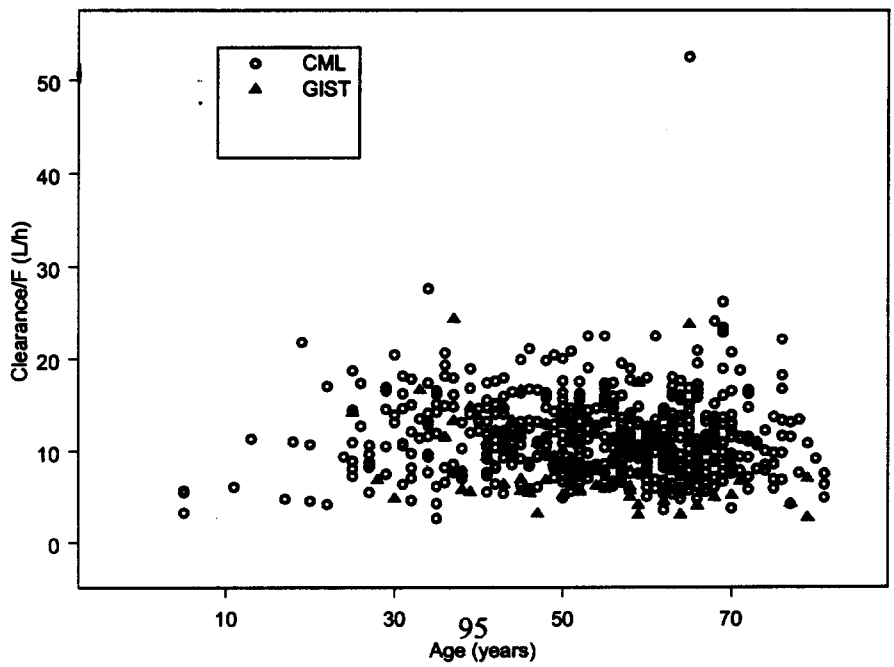
The median CL/F values in patients with GIST and CML is presented in Figure 1. The slightly lower clearance estimated in patients with GIST compared to CML patients is not considered significant and is probably a result of lower number of patients and sparse sampling. The interindividual variability in CL/F in GIST patients was 50%.

**Figure 1: Box plot of CL/F values of Gleevec in patients with GIST and CML**




The similarity in CL/F of Gleevec in the 2 patient populations, GIST and CML, are further supported by Figure 2, where it is evident that over a wide age range the CL/F values in patients with GIST and CML are superimposable.

**Figure 2: CL/F values of Gleevec in patients with GIST and CML**



**Distribution:**

The V/F values estimated in patients with GIST and CML were comparable. The typical value of V/F obtained by the sponsor in patients with GIST was 186 L for an individual with baseline albumin concentration of 38 g/L and baseline bilirubin concentration of 10 g/L. The pharmacometrics reviewer's analysis yielded a typical value for V/F of 178 L in GIST. These values are comparable to the typical V/F value of 213 L obtained in CML patients.

Protein binding of Gleevec was not evaluated in GIST patients.

What, if any, is the effect of patient covariates on PK parameters, CL/F and V/F, of Gleevec in GIST patients?
Are they comparable to the covariates identified in CML patients in the original NDA?

The sponsor's mixed effects modeling of patient covariates (**Appendix** IV) identified baseline WBC and albumin as significant patient covariates which affect CL/F of Gleevec in GIST with the following equation: $CL = 8.48\ (WBC/7.10^{9})^{-0.284} \cdot (albumin/38)^{+1.29}$ (L/h). Increasing baseline WBC decreased CL/F, while increasing baseline albumin increased CL/F. Also, the sponsor has identified baseline albumin and bilirubin as significant covariates which affect V/F of Gleevec in GIST, with the following equation: $V/F = 186\ (albumin/38)^{+1.55} \cdot (bilirubin/10)^{-0.211}$ (L). Increasing baseline albumin values increased V/F, while increasing bilirubin decreased V/F. Addition of a covariate to the model was based a significance level of 0.01 determined by the $\chi^2$ distribution, that is a difference of greater than 6.63 in the NONMEM objective function (-2 x log likelihood).

The sponsor used a model with correlated interindividual variability in CL/F and V/F (omega block(2)) as the base model instead of a diagonal intersubject covariance model. The reviewer concurs that use of omega block (2) results in a significant decrease in objective function and was therefore used by the reviewer as the base model as well.

Using the sponsor's criteria for selection of a covariate, the reviewer's NONMEM analysis (**Table** 1) found that none of the patient covariates tested affected CL/F of Gleevec in GIST. The interindividual variability in CL/F was 50%.

Only baseline albumin was identified as a significant covariate which affected V/F of Gleevec in GIST with the following equation: V/F = 178 + (Albumin-38)*3.71 (L). The interindividual variability in V/F decreased from 47.22% to 41.5% with the addition of baseline albumin as a covariate.

**Table 1: Analysis of effect of patient covariates on CL/F and V/F of Gleevec in patients with GIST.**

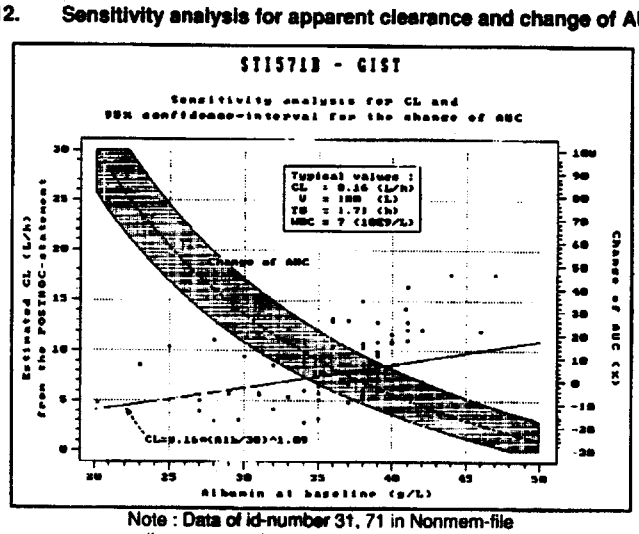
| | | REVIEWER | | | SPONSOR |
|---|---|---|---|---|---|
| **Covariate** | **PK Para-meter** | **OBJ FUNC.** | **Δ OBJ FUNC.** | **Sig-nificance** | **OBJ FUNC.** |
| | | | | | |
| **Base Model** | | **369.116** | | | **371.4** |
| Body Weight | CL/F | 369.106 | -0.016 | NS | |
| Age | CL/F | 368.101 | -1.015 | NS | |
| SGPT | CL/F | 368.012 | -1.104 | NS | |
| SGOT | CL/F | 367.179 | -1.937 | NS | |
| Hemoglobin | CL/F | 369.114 | -0.002 | NS | |
| WBC | CL/F | 365.409 | -3.707 | NS | |
| Bilirubin | CL/F | 369.798 | -0.682 | NS | |
| Albumin | CL/F | 369.078 | -0.038 | NS | |
| | | | | | |
| Body Weight | V/F | 368.254 | -0.862 | NS | |
| Age | V/F | 368.222 | -0.894 | NS | |
| SGPT | V/F | 368.335 | -0.781 | NS | |
| SGOT | V/F | 368.957 | -0.159 | NS | |
| Hemoglobin | V/F | 365.635 | -3.481 | NS | |
| Bilirubin | V/F | 364.425 | -4.691 | NS | |
| Albumin **(FINAL MODEL)** | V/F | 361.617 | -7.49 | ** | 362.4 |
| | | | | | |
| | | | | | |
| Bilirubin + Albumin | V/F | 356.958 | -12.158 | NS | |
| | | | | | |
| **Combined** | | | | | |
| Age | CL/F and V/F | 358.269 | -10.847 | NS | |
| Albumin | CL/F and V/F | 352.875 | -16.241 | ** | 350.5 |
| WBC | CL/F and V/F | 354.189 | -14.927 | ** | |
| Bilirubin | CL/F and V/F | 364.254 | -4.862 | NS | |
| | | | | | |

NS=not significant; **=significant ($p<0.01$)

Since the sponsor's analysis identified bilirubin as a covariate that affected V/F, the effect of both bilirubin and albumin on V/F were tested by the reviewer. However, bilirubin was found to be not significant.

The sponsor's covariate analysis indicated that baseline WBC was a significant parameter that affected CL/F in GIST (Figure 3). This is probably a artifact of high interindividual variability in CL/F and the less number of patients studied.

**Figure 3: Effect of baseline WBC on AUC of Gleevec in patients with GIST.**



Note : Data of id-number 31, 71 in Nonmem-file
(i.e., centre/sub : 501/77, 503/57) excluded.

The reviewer's covariate analysis assessed the effect of WBC simultaneously on both CL/F and V/F. It was interesting that baseline WBC did not significantly affect CL/F or V/F individually but was found to be significant when tested on both CL/F and V/F simultaneously. From a physiology point of view it is difficult to support the idea that baseline WBC affects CL/F of Gleevec. This is further supported by CML patient data from the original NDA which encompasses a wider range of WBC values (up to 250 x $10^9$/L) and also contained many more patients (Figure 4a and 4b).

**Figure 4a and 4b: Effect of baseline WBC on interindividual variability of CL/F values of Gleevec in patients with CML**

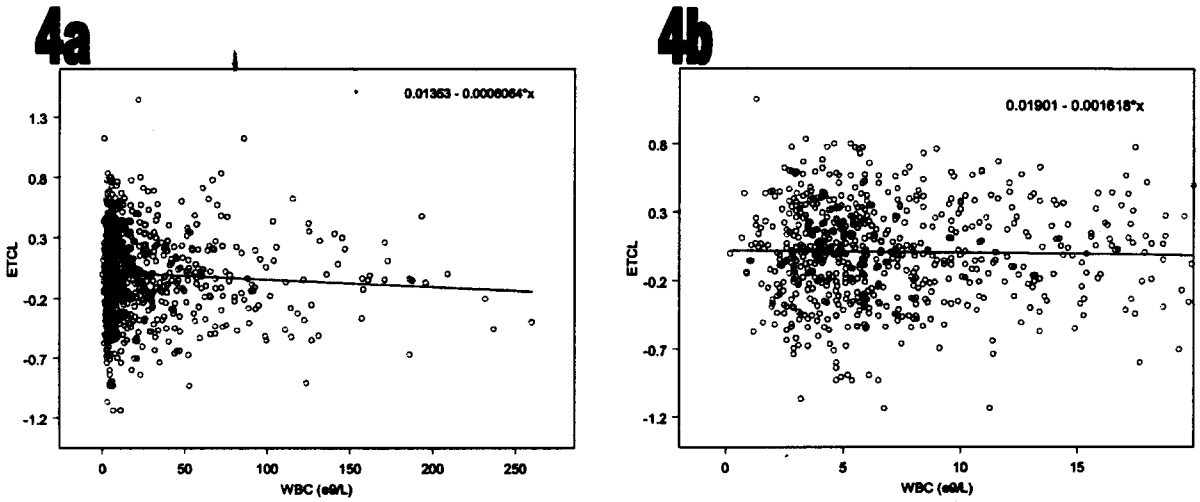


Figure 4 clearly demonstrates the lack of effect of baseline WBC on CL/F in patients with CML. Figure 4b is a zoomed-in version of Figure 4a. Figure 4b illustrates the lack of effect of baseline WBC over the normal range of WBC concentrations.

As seen with baseline WBC, simultaneous testing of effect of albumin on both CL/F and V/F was found to be significant while individually baseline albumin only affected V/F.
It is interesting to note that age and body weight which were identified as significant covariates in the original NDA were not significant in the present analysis. This is probably due to several factors such as less number of patients with GIST, sparse sampling and high inter individual variability and most importantly narrower weight/age ranges.

The final population PK parameter estimates of Gleevec and their standard errors in patients with GIST are presented in Table 2.

Table 2: Population PK parameter estimates of Gleevec in patients with GIST.

| | CL<br>L/h | V<br>L | Tinf<br>h | *Albumin*<br>g/L |
|---|---|---|---|---|
| Mean | 8.07 | 178 | 1.69 | 3.71 |
| SE (%) | 6.3 | 5.6 | 8.1 | 23.1 |
| IIV (% CV) | 50.20 | 41.47 | NA | |
| SE (%) | 16.0 | 19.7 | NA | |
| CORR(CL,V) | 0.884 | | | |
| Residual Error | 38.6%<br>(proportional) | 4.38 mg/L<br>(additive) | | |
| SE (%) | 11.1 | 84.4 | | |

## LABELING

Based on the similarity of CL/F and V/F values in patients with GIST and CML. The pharmacometrics reviewer recommends the following statement in the **CLINICAL PHARMACOLOGY**/Pharmacokinetics section of the label.

***"The pharmacokinetics of imatinib in GIST and CML patients are similar."***

## SUMMARY

1. **The pharmacokinetics of Gleevec in patients with GIST and CML were similar.**
2. **The typical values of CL/F and V/F of Gleevec in GIST patients were 8.07 L/h and 178 L, respectively.**

3. **Only baseline albumin was identified to have a significant effect on V/F of Gleevec. The equation describing the effect of baseline albumin is V = 178 + (Albumin-38)*3.71 (L). This means that V/F of Gleevec is expected to increase by 3.71 L for every 1 g/L increase in albumin above 38 g/L. This is not expected to translate into any dose adjustment.**
4. **None of the patient covariates tested affected CL/F of Gleevec independently.**
5. **The Cmax values estimated in patients with GIST in the present study might not be the true Cmax value because of the limited samples collected and is expected to be highly dependent on the sampling time. This in turn is expected to introduce error in AUC estimation and thus CL/F.**
6. **Patient ID = 13 was not considered to be at steady-state by the sponsor following multiple dosing. The reason of this conclusion is unclear.**

# APPENDIX I

**Parameter estimates and their standard errors from the population pharmacokinetic models fitted to the full data set.**

| Parameter | | Full data (n=73) | | Unit |
|---|---|---|---|---|
| Name | Theta in Nonmem | Estimate | Std. Error | |
| TV of Cl/f | 1 | 8.48 | 0.487 | [L/h] |
| TV of V/f | 2 | 186 | 9.78 | [L] |
| TV of $T_0$ | 3 | 1.70 | 0.139 | [h] |
| Albumin on Cl/f | 12 | 1.29 | 0.383 | |
| WBC on Cl/f | 9 | -0.284 | 0.0758 | |
| Albumin on V/f | 22 | 1.55 | 0.393 | |
| Bilirubin on V/f | 24 | -0.211 | 0.0535 | |
| $\sigma_1$ | 4 | 0.00399 | 0.000160 | [mg/L] |
| $\sigma_2$ | 5 | 0.391 | 0.0206 | |
| $\Omega_{11}$ | | 0.166 | 0.0341 | |
| $\Omega_{21}$ | | 0.138 | 0.0331 | |
| $\Omega_{22}$ | | 0.150 | 0.0335 | |

*C.*

## *APPENDIX II*

```
THETA:   CL      V       D1      ALB_V
ETA:
ERR:
k0albv.lst  361.616     eval=269 sig=3.7 sub=73 obs=489 CCIL=YNYN NV1.1 PIV1.1
THETA   = 8.07      178       1.69      3.71
ETASD   = 0.501996  0.414729  0c
ETAR12  = 0.884
ERRSD   = 0.386005  0.0438178
THETA:se% = 6.3     5.6       8.1       23.1
OMEGA:se% = 16.0    19.7      0.0c
SIGMA:se% = 11.1    84.4

MINIMIZATION SUCCESSFUL


 user 0:57.5            real 0:57.5  tcl 0:4.23

$PROBLEM TRUE MODEL => SIMULATION
$INPUT WT WBC CREA SGPT SGOT HGB ALB BIL AMT EVID TIME MDV
$INPUT ID SS II DV RATE SEX LC AGE SUB=DROP CNTR=DROP

$DATA ..\Orig_PK.PRN IGNORE=C

$SUB ADVAN1 TRANS2

$PK
   FALB  = ALB-38
   FAGE  = AGE-50
   FWBC  = WBC-10
   FWT   = WT-75
   FBIL  = BIL-10

   TVCL  = THETA(1)
   TVV   = THETA(2)+FALB*THETA(4)
   TVD1  = THETA(3)

   ETCL  = ETA(1)
   ETV   = ETA(2)
   ETD1  = ETA(3)

   CL    = TVCL*EXP(ETCL)
   V     = TVV *EXP(ETV)
   D1    = TVD1*EXP(ETD1)

   S1    = V

$ERROR
    Y=F*EXP(ERR(1))+ERR(2)

$THETA
   (0,10)       ; CL
   (0,200)      ; V
   (0,1,10)     ; D1
   (-10,-0.09,10) ; ALB_V

$OMEGA BLOCK(2)
   0.09
   0.04 0.09

$OMEGA 0 FIX

$SIGMA
   0.04
   0.2

$EST METH=1 INTER MAXEVAL=9999 PRINT=5 NOABORT

$COV

$TABLE ID SEX LC AGE WT WBC CREA SGPT SGOT HGB ALB BIL AMT EVID
     ETCL ETV ETD1 CL V D1 TIME Y NOPRINT ONEHEADER FILE=k0albv.fit
```

*D. APPENDIX III*

Population PK parameter estimates of imatinib in patients with CML.

| | 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 (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'.***

# APPENDIX IV

**Table 6-2. Summary of building the population PK model**

| Residual Model | Intersubject Covariance Model | Covariates for Cl/f | Covariates for V/f | −2 · log likelihood |
|---|---|---|---|---|
| Proportional | Zero | | | 1878.3 |
| Additive | Zero | | | 905.7 |
| Add.+Prop. | Zero | | | 804.1 |
| Add.+Prop. | Cl/f | | | 648.0 |
| Add.+Prop. | Diagonal:(Cl/f, V/f) | | | 430.2 |
| Add.+Prop. | Block: (Cl/f, V/f) | | | 371.4 |
| Add.+Prop. | Block: (Cl/f, V/f) | | **Albumin** | 362.4 |
| Add.+Prop. | Block: (Cl/f, V/f) | **Albumin** | | 350.5 |
| Add.+Prop. | Block: (Cl/f, V/f) | | **Bilirubin** | 341.3 |
| Add.+Prop. | Block: (Cl/f, V/f) | **WBC** | | 332.3 |

# Secondary Pharmacometrics Review

| | |
|---|---|
| **NDA:** | **21-335** |
| **Volume:** | **13 of 14 volumes** |
| **Compound:** | **Glivec (imatinib mesylate)** |
| **Submission Date:** | **October 15, 2001, S-01** |
| **Applicant:** | **Novartis Pharmaceuticals Corp.** |
| **Team Leader:** | **Joga Gobburu** |

Background

**The sponsor submitted a population analysis report to describe pharmacokinetics of Gleevec in Gastrointestinal stromal tumor (GIST) patients. Drs. Robbie and Williams, Office of Clinical Pharmacology and Biopharmaceutics, independently reviewed the population analysis report. This secondary review will summarize the conclusions arrived by the Drs. Robbie and Williams and present the final recommendations.**

The final model (one-compartment model with a zero-order absorption) presented by the sponsor included the effects of baseline WBC and baseline albumin levels as covariates for clearance, and baseline bilirubin and baseline albumin as covariates for volume of distribution. Dr. Williams explored several other covariates including body weight, age and sex to describe the variability in the PK parameters. His review points to the lack of obvious biological plausibility for the selected covariates. The sponsor did not provide any rationale for the inclusion of WBC to describe clearance, nor did the sponsor provide any explanation for why the volume of distribution decreases with higher baseline albumin levels.

Dr. Robbie's review also points to the important issue about the sponsor's final model, which is the lack of sound rationale for the selection of the covariates. Systematically evaluating the covariates (body weight, age, SGPT, SGOT, Hemoglobin, WBC, bilirubin, albumin) one at a time did not show any significant relationships (except for albumin on volume). However, Dr. Robbie found that simultaneous inclusion of albumin or WBC on clearance and volume of distribution resulted in significant correlation. His review showed that baseline WBCs did not have any effect on clearance in CML patients (N=546). Further, he noted that the PK parameter estimates of Gleevec in GIST patients are similar to that in chronic myeloid leukemia (CML) patients.

Overall, the unexplained variability is considerably high with or without covariates. Hence the sponsor's or the reviewers' model provides only the central tendency of the PK parameters and not adequate information to individualize the dosing, if necessary.

Recommendations

**Based on the independent reviews of Drs. Robbie and Williams, the Office of Clinical Pharmacology and Biopharmaceutics recommends the following labeling statement to be added to the CLINICAL PHARMACOLOGY/Pharmacokinetics section of the labeling:**

**The pharmacokinetics of imatinib in GIST and CML patients are similar.**

Comments to be forwarded to the sponsor:

**The following comments should be forwarded to the sponsor:**

1. **Due to the lack of biological plausibility the sponsor's final model cannot be accepted. The sponsor is encouraged to consider mechanistically relevant covariates during model building in future.**
2. **Patient NONMEM ID=13 was not considered to be at steady-state even after 873 h post dosing, as per the data submitted to the agency. The reason for this is not clear.**
3. **The Pharmacometrics group at the Office of Clinical Pharmacology and Biopharmaceutics, CDER, FDA, welcomes scientific discussions with sponsors on model building strategies both at the protocol stage as well as during modeling.**

/S/

Jogarao Gobburu, Ph.D.
Team Leader,
Pharmacometrics,
Division of Pharmaceutical Evaluation –1, HFD-860,
Office of Clinical Pharmacology and Biopharmaceutics,
CDER, FDA.

## *VI. Appendix D. – Cover Sheet and OCPB Filing/Review Form*

## IX. *Office of Clinical Pharmacology and Biopharmaceutics*

## *New Drug Application Filing and Review Form*

General Information About the Submission

| | Information | | Information |
|---|---|---|---|
| **NDA Number** | **21335 SE1** | **Brand Name** | **Gleevec** |
| **OCPB Division (I, II, III)** | **I** | **Generic Name** | **imatinib** |
| **Medical Division** | **DODP** | **Drug Class** | protein-tyrosine kinase inhibitor |
| **OCPB Reviewer** | **Gene Williams** | **Indication(s)** | **gastro-intestinal stromal tumor (GIST)** |
| **OCPB Team Leader** | **N.A.M. Atigur Rahman** | **Dosage Form** | **50 & 100 mg capsules** |
| | | **Dosing Regimen** | **QD** |
| **Date of Submission** | **10/15/01** | **Route of Administration** | **oral** |
| **Estimated Due Date of OCPB Review** | **12/21/01** | **Sponsor** | **Novartis** |
| **PDUFA Due Date** | **April 15, 2001** | **Priority Classification** | **1P** |
| **Division Due Date** | **12/31/01** | | |

*Clin. Pharm. and Biopharm. Information*

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments if any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | x | | | |
| **Tabular Listing of All Human Studies** | x | | | |
| **HPK Summary** | x | | | |
| **Labeling** | x | | | |
| **Reference Bioanalytical and Analytical Methods** | x | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| *Healthy Volunteers-* | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| *X. Patients-* | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | x | 1 | 1 | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | x | 1 | 0 | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |

| | | | | |
|---|---|---|---|---|
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | x | 1 | 1 | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | [redacted] | 3 | 2 | |
| *B.* | | | | |
| *C. Filability and QBR comments* | | | | |
| | **"X" if yes** | | | |
| **Application filable ?** | x | | | |
| **Comments sent to firm ?** | | | | |
| **QBR questions (key issues to be considered)** | **Is PK different between CML (prior approval) and GIST (current application)?** | | | |
| **Other comments or information not included above** | | | | |
| **Primary reviewer Signature and Date** | **Gene M. Williams 12/20/01** | | | |
| **Secondary reviewer Signature and Date** | **N.A.M. Atiqur Rahman 12/21/01** | | | |

## *VI. Appendix E. – Review of NDA 21-335 for CML*

## XI. *Office of Clinical Pharmacology and Biopharmaceutics*

## *New Drug Application Filing and Review Form*

General Information About the Submission

| | Information | | Information |
|---|---|---|---|
| **NDA Number** | **21-335** | **Brand Name** | **Gleevec** |
| **OCPB Division (I, II, III)** | **I** | **Generic Name** | **Imatinib mesylate/STI571** |
| **Medical Division** | **HFD-150** | **Drug Class** | **Oncology Drug** |
| **OCPB Reviewer** | **John Duan, Joga Gobburu** | **Indication(s)** | **CML** |
| **OCPB Team Leader** | **Atiqur Rahman** | **Dosage Form** | **Hard Gelatin** |
| | | **Dosing Regimen** | **400 mg, QD, 600 mg, QD** |
| **Date of Submission** | **2/27/2001** | **Route of Administration** | **Oral** |
| **Estimated Due Date of OCPB Review** | **4/26/2001** | **Sponsor** | **Novartis** |
| **PDUFA Due Date** | **8/27/2001** | **Priority Classification** | **Priority** |
| **Division Due Date** | **4/27/2001** | | |

*Clin. Pharm. and Biopharm. Information*

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | X | | | |
| **Tabular Listing of All Human Studies** | X | | | |
| **HPK Summary** | X | | | |
| **Labeling** | X | | | |
| **Reference Bioanalytical and Analytical Methods** | X | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | X(107) | 1 | 1 | |
| **Isozyme characterization:** | X | 9 | 9 | |
| **Blood/plasma ratio:** | X | 1 | 1 | |
| **Plasma protein binding:** | X | 4 | 4 | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| *Healthy Volunteers-* | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| *XII. Patients-* | | | | |
| single dose: | | | | |
| multiple dose: | X(03001) | 1 | 1 | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | X | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | X(119) | 1 | 1 | |
| In-vivo effects of primary drug: | X(118) | 1 | 1 | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| Ethnicity: | | | | |
| Gender: | | | | |
| Pediatrics: | | | | |
| Geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | X(03001) | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | X(102) | 1 | 1 | |
| Data sparse: | X(109,110) | 1 | 1 | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | **X(108)** | 1 | 1 | |
| **Relative bioavailability -** | | | | |

| | | | | |
|---|---|---|---|---|
| solution as reference: | X | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | X | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | X(109,110) | 1 | 1 | |
| **Dissolution:** | X | 4 | 4 | |
| (IVIVC): | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | X | 7 | 7 | |
| **Total Number of Studies** | | 26 | 26 | |
| *D.* | | | | |

*E. Filability and QBR comments*

| | "X" if yes | |
|---|---|---|
| **Application filable ?** | X | |
| **Comments sent to firm ?** | X | |
| **QBR questions (key issues to be considered)** | | 1. **How is Gleevec metabolized? What is the clinical relevance of its metabolism?**<br>2. **Is there any food effect on Gleevec?**<br>3. **Is the formulation change acceptable?**<br>4. **Is the proposed replacement of dissolution testing with disintegration time acceptable?** |
| **Other comments or information not included above** | | |
| **Primary reviewer Signature and Date** | **John Duan, Joga Gobburu** | |
| **Secondary reviewer Signature and Date** | **Atiqur Rahman** | |

CC: NDA 21-335, HFD-850 (Lee), HFD-150(Stanten), HFD-860 (Rahman, Mehul, Sahajwalla), CDR

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| **NDA 21-335** | **Submission Date:** February 27, 2001<br>April 10, 2001<br>April 12, 2001 |
| **Drug Name:** | GLEEVEC™ (imatinib, CGP 57148B, STI 571) |
| **Formulation & Strength:** | Oral Hard Gelatin Capsule, 50 and 100 mg |
| **Applicant:** | Novartis Pharmaceutical Corp.<br>59 Route 10<br>East Hanover, NJ 07936 |
| **Reviewer:** | John Duan, Ph.D. |
| **Pharmacometrics Reviewer:** | Jogarao Gobburu |
| **Type of Submission:** | New Drug Application |

This is a review of the Clinical Pharmacology and Biopharmaceutics (CPB) studies submitted in NDA 21-335 in support of GLEEVEC™ indicated for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

## I. OVERALL SUMMARY

The applicant has submitted 26 studies in Section 6 (Human Pharmacokinetics and Bioavailability) of this NDA to seek an approval for GLEEVEC indicated for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. The recommended dose is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis and the doses may be increased to 600 mg and 800 mg, respectively, based on tolerance and disease states.

GLEEVEC™ (imatinib mesylate) is a protein-tyrosine kinase inhibitor, which selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia (CML).

Nonlinear mixed effects pharmacokinetic modeling suggested that body weight and age are the important covariates governing the exposure of imatinib. The WBC counts decrease over time in a concentration dependent manner. No exposure (dose or concentration) – desired effect relationships could be derived for the pharmacodynamic variables – survival and time to (hematologic/cytogenetic) response. A imatinib steady –

state concentration and probability of edema relationship was established. Older CML patients are identified to be the sub-population that is most prone to grade 3 or higher edema..

After oral administration, imatinib was absorbed with the $C_{max}$ between 2 and 4 hours. Although Caco-2 cell monolayer transport studies conducted at low drug concentrations showed the drug to be a low permeability drug, the absolute bioavailability of the drug was 98%. Therefore, imatinib is classified as a high permeable drug. At clinically relevant concentrations of imatinib, binding of the parent drug to plasma proteins was approximately 95%, mostly to albumin and $\alpha_1$-acid glycoprotein. However, the protein binding of the major active metabolite CGP74588 was not studied. Following oral administration, the elimination half life of the parent drug and the major metabolite, CGP74588 were approximately 18 and 40 hours, respectively. Imatinib AUC was dose proportional at the recommended dose range. Approximately 81% of the dose was eliminated within 7 days, 68% in feces and 13% in urine. The main circulating active metabolite in humans was the N-demethylated piperazine derivative CGP74588 that showed similar in vitro potency as the parent drug. The plasma AUC of this metabolite was 16% of the AUC for imatinib. CYP3A4 was the major enzyme responsible for the metabolism of imatinib. Imatinib exposure increased significantly when GLEEVEC was co-administered with a single 400 mg dose of ketoconazole. A preliminary report showed that imatinib increased the mean $C_{max}$ and AUC of simvastatin (CYP3A4 substrate). Both STI571 and CGP74588 appear to be potent inhibitors of CYP2D6. Therefore, there is a potential for drug interactions between STI571 and CYP2D6 related drugs. There are no pharmacokinetic data in pediatric patients although a study is ongoing. No clinical studies were conducted with GLEEVEC in patients with impaired renal or hepatic functions. However, caution should be exercised when Gleevec is administrated to patients with hepatic function impairment. The effects of food on the bioavailability of STI 571 have been evaluated in patients at steady state. Adequate dissolution data were provided.

From Clinical Pharmacology and Biopharmaceutics perspective, the NDA is acceptable. However, reports of ongoing studies and final report of study 0118 should be submitted for review and labeling update. In addition, a drug interaction study between imatinib and CYP2D6 related drugs is recommended as a Phase IV commitment. Since hepatic elimination is the major elimination pathway for Gleevcc and no dose recommendation can be made for patients with liver impairment, a clinical study to evaluate the pharmacokinetics of imatinib in liver impaired patients as a Phase IV commitment is recommended. Further, although the exposure to the major metabolite CGP74588 is 16% of the parent drug, the definite contribution of this metabolite to the overall activity of Gleevec can not be concluded in absence of the plasma protein binding information of the metabolite.. Therefore, the protein binding of this active metabolite should be assessed as a Phase IV commitment.

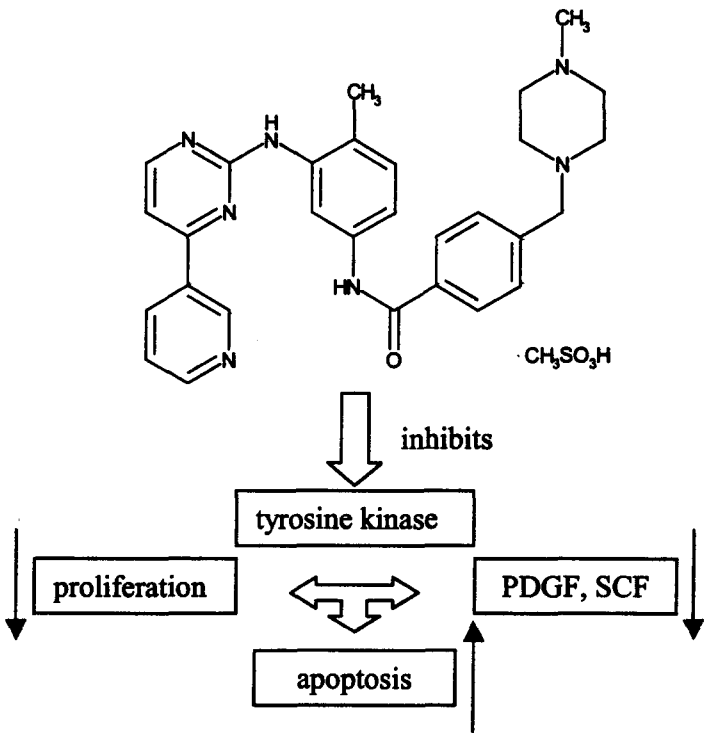
# II. TABLE OF CONTENTS

This Review is TAKen from orig NDA + is on the web Redacted exactly as on the web

## III. BACKGROUND

General

GLEEVEC™ (imatinib mesylate) is a pr[illegible] which potently inhibits
the Bcr-Abl tyrosine kinase.

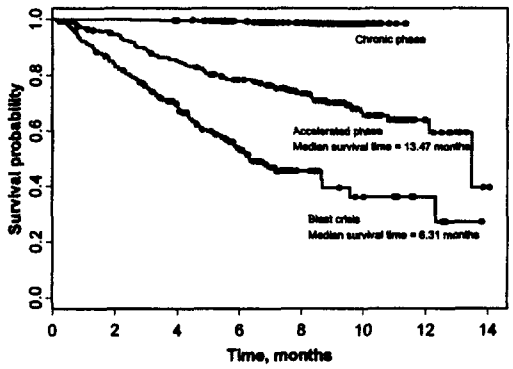



The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia (CML) and acute lymphoid leukemia (ALL) patients. In addition, imatinib is a potent inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events.

The applicant has submitted the following studies in Section 6 (Human Pharmacokinetics and Bioavailability) of this NDA to seek an approval for GLEEVEC indicated for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

| Studies submitted | No. of studies | Number of Subjects | | Dose range |
|---|---|---|---|---|
| | | Patients | Healthy volunteers | |
| Dose finding study | 1 | 591 | 33 | 25-1000 mg |
| Mass balance study | 1 | | | |
| Bioavailability study | 1 | | | |
| Food effect study | 1 | | | |
| Drug interaction studies | 2 | | | |
| PK/PD study | 1 | | | |
| Population pharmacokinetic study | 1 | | | |
| in vitro protein binding studies | 5 | | | |
| In vitro metabolism studies | 9 | | | |
| Dissolution studies | 4 | | | |
| Literature references | 7 | | | |

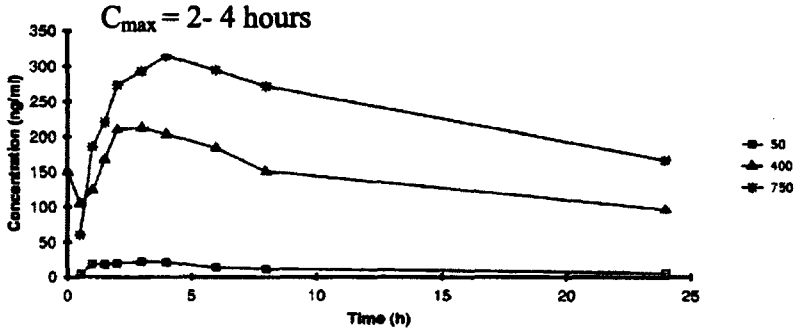
The survival of the patients could not be correlated with the concentration/dose. The time to (hematologic/cytogenetic) response, also, could not be correlated with the concentration/dose. The survival probability curves of the CML patients in the 3 different disease states are shown below:



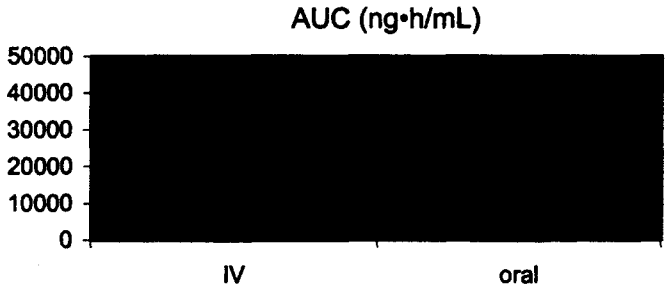

The median survival time for the patients in accelerated and blast crisis were estimated to be 13.47 and 6.31 months, respectively. The fact that most of the patients in blast crisis received 600 mg (and not lower doses) complicates the interpretation. Further, the dose and/or the concentration range is quite narrow and given that the doses are chosen to produce maximum peripheral WBC count suppression, limits the probability of establishing the relationship in the first place.

A clear concentration – probability of developing edema relationship was found. The figure below shows the probability of having a grade 3 edema in blast crisis patients. Older patients (age >= 65 years) are most prone to edema.

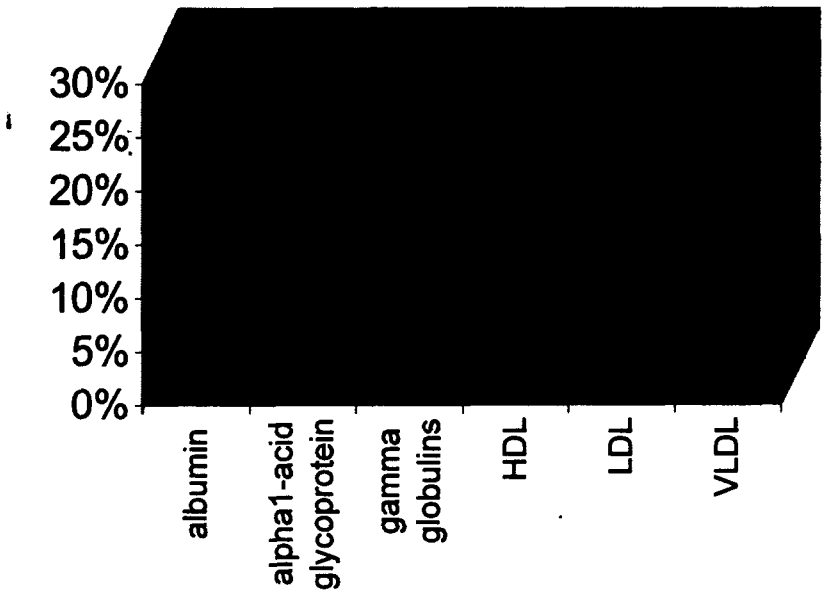
Imatinib was absorbed with the $C_{max}$ being 2-4 hours as shown in the figure below (a typical STI571 concentration vs. time profile).




Mean absolute bioavailability for the capsule formulation is 98%. The coefficient of variation for plasma imatinib AUC is in the range of 40-60% after an oral dose. Following is a comparison of AUC between IV and oral dosing.




At clinically relevant concentrations of imatinib, binding to plasma proteins is approximately 95% on the basis of *in vitro* experiments, mostly to albumin and $\alpha_1$-acid glycoprotein, with little binding to lipoprotein as shown in the following figure.

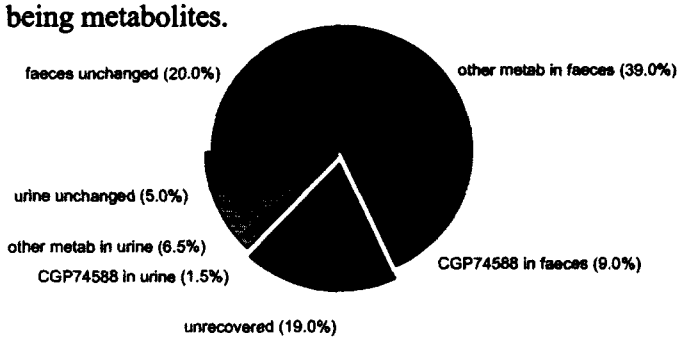


As shown in the table below, in vitro studies showed concentration dependent human plasma protein binding.

| Concentration in plasma | % bound | Study |
|---|---|---|
| µg/mL | 95% | DMPK(F) 1998/035 |
| µg/mL | 93% | DMPK(F) R99-010 |
| µg/mL | 91% | BPK(CH)1995/116 |
| µg/mL | 86% | DMPK(F) 1998/035 |

The main circulating metabolite in humans is the N-demethylated piperazine derivative CGP74588 which shows similar *in vitro* potency as the parent. The plasma AUC for this metabolite was found to be 16% of the AUC for imatinib.

Based on the recovery of compound(s) after an oral $^{14}C$-labelled dose of imatinib, approximately 81% of the dose was eliminated within 7 days in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

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# IV. QUESTION BASED REVIEW

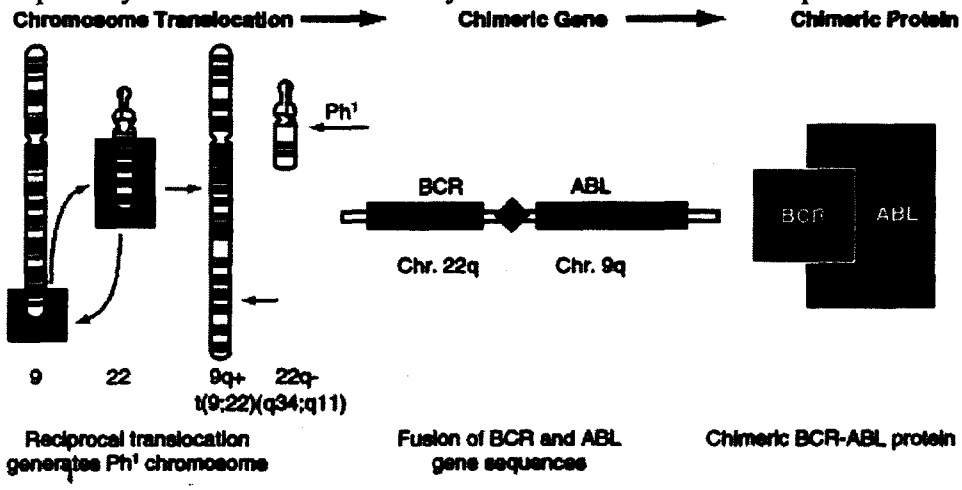
This review is completed by using the Question Based Review approach.

### *1. What is CML? How does STI571 work?*

The diagnosis of CML is established by identifying cytogenetically or molecularly a clonal expansion of a hematopoietic stem cell possessing a reciprocal translocation between chromosomes 9 and 22. This translocation results in the head-to-tail fusion of the breakpoint cluster region (Bcr) gene on chromosome 22 at band q11 with the Abl (named after the abelson murine leukemia virus) gene located on chromosome 9 at band q34 as shown in the following figure. The fusion of these DNA sequences allows the generation of an entirely novel fusion protein with modified function. The consequence of expression of the *Bcr-Abl* gene product is the activation of signal transduction pathways, leading to cell growth independent of normal external growth factor signals.

The disease is characterized by the inevitable transition from a chronic phase (median survival: 60-89 months) to an accelerated phase (median survival: <18 months) and on to blast crisis (median survival: 3-6 months).

Imatinib potently inhibits the Bcr-Abl tyrosine kinase. It inhibits proliferation and




induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia (CML) patients. In addition, imatinib is a potent inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events.