Clinical Pharmacology Review

NDA	21-588
Submission Date	016: March 27, 2006, July 7, 2006
Brand Name	Gleevec®
Generic Name	imatinib mesylate
Formulation	100 and 400 mg tablets
Reviewer	Julie M. Bullock, Pharm.D.
Team Leader	Brian Booth, Ph.D.
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OCPB Division	Division of Clinical Pharmacology V
ORM Division	Division of Drug Oncology Products
Sponsor	Novartis Pharmaceuticals
Submission Type; Code	Supplemental NDA; 016
Indication	016: Newly diagnosed pediatric patients with Ph+ CML
Dosing regimen	340 mg/m^2/day (not to exceed 600 mg)

An Optional Inter-division briefing was held on September 21, 2006

Table of contents

List of Tables

List of Figures

1 Executive Summary

Gleevec (imatinib mesylate) is a tyrosine kinase inhibitor that has been previously approved by the agency for the treatment of chronic myeloid leukemia (CML) and for the treatment of patients with Kit (CD117) positive metastatic and/or unresectable malignant gastrointestinal stromal tumors (GIST). Gleevec was also approved in 2003 for use in children with Ph+ chronic phase CML which was recurrent after stem cell transplantion or who are resistant to interferon-alpha therapy.

In the present sNDA submission, the applicant is requesting approval for treatment of newly diagnosed pediatric patients with Ph+ CML which will fulfill the pediatric written request for Gleevec. The written request was issued to the sponsor on Sept 12, 2000.

The sponsor collected intensive pharmacokinetic samples in the phase 1 studies STI571A 0103 and STI571A 03 001, and sparse sampling was gathered in study STI571A 2108. Both phase 1 studies evaluated a range of doses in pediatric patients to obtain a dose that had similar exposure to adults. In the phase 2 study 53 pediatric patients with newly diagnosed CML were enrolled and dosed with of 340 mg/m^2/day. Thirty-three of these patients had sparse sampling to determine pharmacokinetics. With the completion of the three trials above the applicant has met the requirements of the Pediatric Written Request.

The results of the intensive PK sampling in studies 0103 and 03 001 indicate that the pharmacokinetics in pediatrics and in adults are similar based on a comparison of clearance (pediatrics 6.38 ± 48% $L/hr/m^2$, adult 5.78 ± 32% $L/hr/m^2$). Sparse samples were collected in the Phase 2 study and were analyzed using a one-compartment model previously developed for adult patients. Briefly, the pharmacokinetic parameters estimated from the model were comparable to those found in previous studies with pediatric patients with intensive PK sampling.

No significant relationships were found between measures of Gleevec exposure and grade 3/4 toxicity. The incidence of grade 3/4 toxicities was generally less than the incidence of grade 1/2 toxicities for all the common adverse events reported. No significant relationships were found between measures of Gleevec exposure (AUC, average dose, and average dose intensity) and measures of response (cytogenetic and hematologic response) in this population. This may be due to the limited number of patients enrolled and the number of responses that were missing, not assessed, or not available at 3 months when cytogenetic response was assessed.

1.1 Recommendations

The clinical pharmacology information provided in this supplemental NDA is acceptable. No action is indicated.

Reviewer: Julie M. Bullock, Pharm.D. Division of Clinical Pharmacology 5	Acting Team Leader: Brian Booth, Ph.D. Division of Clinical Pharmacology 5

Cc: DDOP: CSO - A Staten; MTL - J Johnson; MO - M Cohen
DCP-5: Reviewer - J Bullock; TL - B Booth; DD - A Rahman

1.2 Clinical Pharmacology Summary

This supplement is based on efficacy and safety data from two previously submitted studies (sNDA 21-335 on June 28, 2002):

- STI571A 0103: A Phase 1, dose-finding, study to determine the safety, tolerability, pharmacokinetic, and pharmacodynamic profiles and to evaluate for anti-leukemic effects of STI571A in pediatric patients with Ph+ leukemia.
- STI571A 03 001: A phase 1, dose-finding study to determine the safety, tolerability and PK/PD profiles, and to evaluate for preliminary anti-leukemic effects of STI571 in patients with CML resistant to interferon..

and one phase 2 study completed by the National Cancer Institutes Children's Oncology group:

- STI571A 2108: A Phase 2 study of Gleevec in pediatric patients with Ph+ chronic phase CML.

Pharmacokinetic data was gathered in each of the studies including intensive (studies 0103 and 03001) and sparse sampling (study 2108). In the phase 2 study, 53 pediatric patients with newly diagnosed CML were enrolled and dosed with 320 mg/m^2/day. The objective of this study was to evaluate the efficacy of Gleevec in this patient population. Thirty-three patients were sampled on Day 1 to determine the pharmacokinetics.

The pharmacokinetics of Gleevec in pediatrics were evaluated using a one-compartment model with first order elimination which had previously been used to characterize adult pharmacokinetics. The clearance and volume models used body weight (in kg), hemoglobin (Hgb), and white blood cell (WBC) count for covariates. The model adequately characterized the pharmacokinetics in the thirty-three pediatric patients as the Cmax and AUC estimated from the data were similar to those reported in previous pediatric studies with intensive pharmacokinetic sampling.

No significant relationships were found between measures of Gleevec exposure (AUC, average dose, and average dose intensity) and measures of response (cytogenetic and hematologic response) in this population. This may be due to the limited number of patients enrolled and the number of responses that were missing, not assessed or not available at 3 months when cytogenetic response was assessed. No significant relationships were found between measures of Gleevec exposure and grade 3/4 toxicity.

The incidence of grade 3/4 toxicities was in general less than the incidence of grade 1/2 toxicities for all the common adverse events reported. Detailed clinical pharmacology and biopharmaceutics information has been previously submitted and reviewed in the original NDA 21-335 (submission of 27-Feb-2001) and NDA 21-588 (submission of 13-Dec-2002)

2 Question Based Review

Imatinib has been reviewed previously under NDA 21-335 for CML (submission of 27-Feb-2001) and GIST (submission of 15-October-2001). NDA 21-588 has the same indications, but is for the tablet formulation instead of the capsule formulation used in NDA 21-335. For brevity, only QBR questions regarding this current supplemental NDA submission will be addressed below. For additional information please see posted clinical pharmacology reviews in the Division File System (DFS).

2.1 General attributes

Previously reviewed, please see posted NDA reviews in DFS.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical studies?

Study 2108 was an open label, multi-center, phase II clinical trial. Patients were stratified into the following groups:

- Stratum 1 = CML in the first chronic phase previously treated with interferon
- Stratum 2 = CML relapsing after transplantation or in 2nd or subsequent chronic phase
- Stratum 3 = newly diagnosed CML in 1st chronic phase, no prior treatment

All patients received the same treatment of 340 mg/m^2/day (rounded to the nearest 100 mg increment) with no interruptions in the absence of dose limiting toxicity. Each 28 day period was defined as a course (see Table 1). Two courses were given in the absence of progressive disease. Pharmacokinetic evaluations were performed during the first course on Days 1 and 2.

TABLE 1: Sponsors outline of the study design.

Pre-study	← Treatment →			
	First course[a)]	Second course[a)]	Subsequent courses[a)]	End of study
Day –30 - 0	Day 1-28	Day 29-56	Days ≥ 57	ongoing
Week –4-0	Week 1-4	Week 5-8	Weeks ≥ 9	ongoing

a) After each course of the first year of treatment a hematological evaluation was performed. Cytogenetic assessment was performed by bone marrow examination at the end of the first cycle (optional), and at the end of the third, sixth, ninth and twelfth courses during the first year of treatment. Patients who were responding to therapy could continue in the absence of significant toxicities.

The co-primary endpoints were:

- To estimate the response rate to Gleevec administered orally once daily without interruption to children with Ph+ CML.
- To determine the disease-free survival of patients treated with Gleevec given on this schedule.
- To characterize the PK behavior of Gleevec in children with Ph+ CML and correlate with response.

- To better delineate toxicities associated with Gleevec administration.

The secondary objectives were to define the rates and the time to achieve hematological, cytogenetic, and molecular response.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how were they measured in the clinical study?

The efficacy criteria were assessed using complete blood counts and bone marrow analyses. Blood counts were measured at study entry and at weekly intervals for the duration of treatment courses 1 and 2, and then repeated at two week intervals for the duration of treatment. Cytogenetic response was measured during the first week of courses 4 and 7, prior to course 10, and during the second year of therapy. If complete cytogenetic response (CCyR) was achieved, analysis for bcr-abl was done to assess the molecular response.

Hematological response was evaluated for each of the first two courses. A hematological response was defined as a reduction of >50 % in baseline white blood cell counts (WBC), which was maintained for at least two weeks. A complete response hematological response was defined as a reduction in the WBC to <10,000 per cubic millimeter and platelets <450,000 per cubic millimeter maintained for four weeks.

Cytogenetic response was defined by percentage of Ph positive metaphases as follows:

- Complete (CCyR): absence of Ph chromosome, with resolution of bone marrow and blood morphologic abnormalities, based on analysis of 20 cells in metaphase, whenever possible. (If the patient had a CCyR, the absence of bcr-abl rearrangement by RT-PCR was considered a complete molecular response)
- Partial (PCyR) 1-35% and greater than 35% at baseline
- Minor 36-65% and greater than 65% at baseline
- Minimal 66-95% and greater than 95% at baseline
- None 96-100%

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Plasma concentrations for STI571 and associated metabolite CGP74588 were determined by high-performance liquid chromatography MS/MS method (LC/MS/MS). The limit of quantification was 4 ng/mL for both analytes. The assay method for Gleevec has been previously reviewed and accepted.

2.2.4 Exposure Response

Of the patients with pharmacokinetics, 23 of the 33 had a hematologic response. The results for cytogenetic response included 13 subjects who had a response of 'NA' (missing, not assessed, or not available), leaving only 20 subjects with a reportable response to Gleevec. The breakdown of subjects hematological response and cytogenetic response is below.

TABLE 2: Breakdown of patients with hematologic and cytogenetic responses from in

pharmacokinetic subset for Study 2108

Hematologic Response		
Yes	No	na
23	8	2

Cytogenetic Response					
Complete	Partial	Minor	Minimal	None	na
8	6	2	2	2	13

Cytogenetic Binary Response		
Major	Minor	na
14	6	13

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

AUC vs. Response:

The AUC vs. response rate analysis includes only those patients who were included in the pharmacokinetic subset (n=33). Because of the limited number of subjects, an exposure response relationship is hard to determine from the results. There were no trends for complete hematological or cytogenetic response with increasing AUC (see Figures 1, 2 and 3)

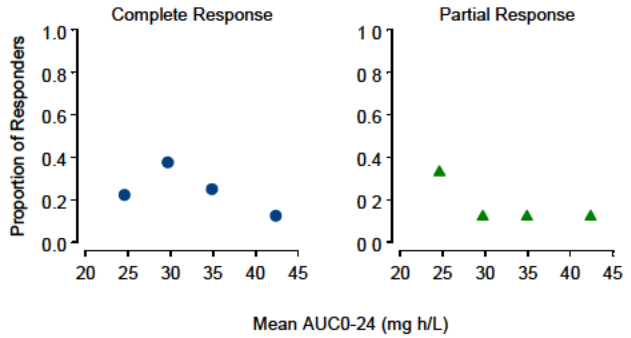

FIGURE 1: Complete and Partial Cytogenetic Response vs. $AUC_{0\text{-}24}$

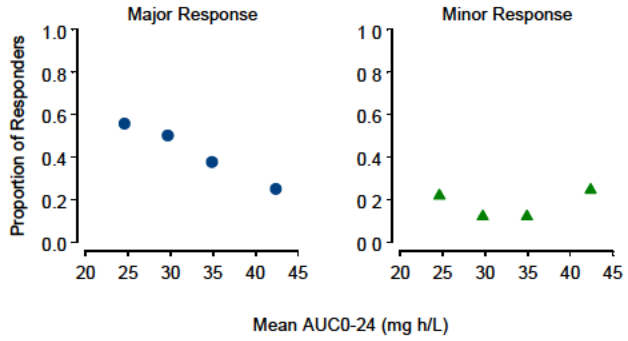

FIGURE 2: Major and Minor Cytogenetic Response vs. AUC_{0-24}

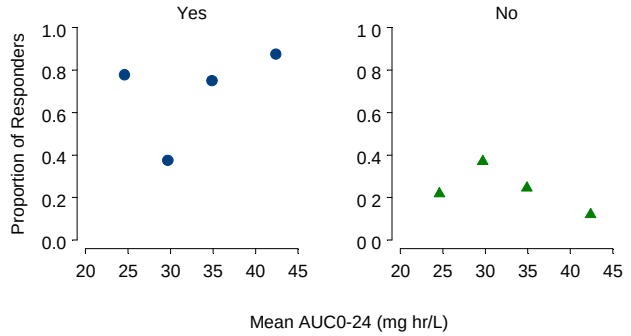

FIGURE 3: Hematologic Response vs. AUC_{0-24}

Average Dosage Intensity vs. Response

The average dose intensity was calculated from the average dose in mg (Total dose received during the study/total exposure days) divided by the patients body surface area (BSA) in m^2. For the complete and partial response analysis, as well as the hematological response analysis, the entire patient population was included (n=53) except for patient 731074. Patient 731074 did not have a record of average dose intensity and therefore was excluded from the dosage vs. response analysis. This patient was noted as having a complete hematological response, a partial cytogenetic response, and was classified as having a major cytogenetic response. Binary cytogenetic responses (major/minor) were only defined for patients in the PK subset therefore that analysis only includes those patients (n=33).

There is no significant difference between hematologic or cytogenetic response and average daily intensity (Figures 4, 5 and 6).

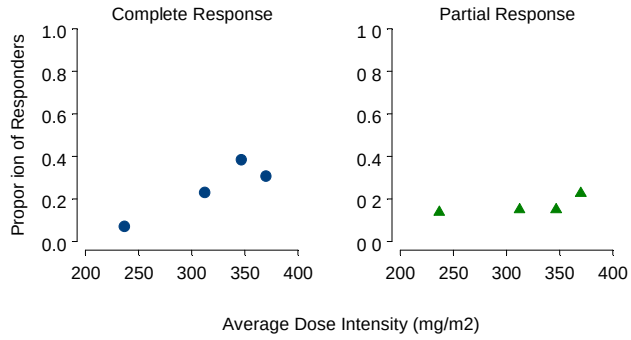

FIGURE 4: Complete, Partial Cytogenetic Response vs. Average dose intensity (n=53)

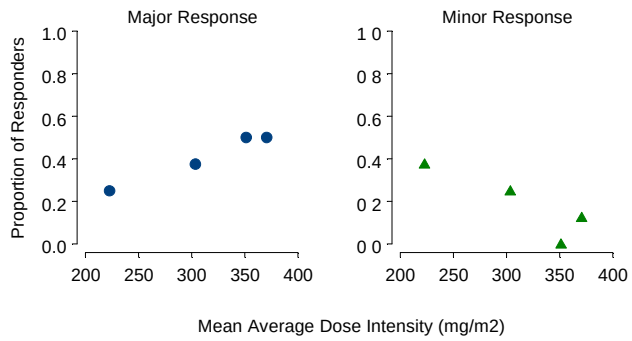

FIGURE 5: Major, Minor Cytogenetic Response vs. Average dose intensity (n=33)

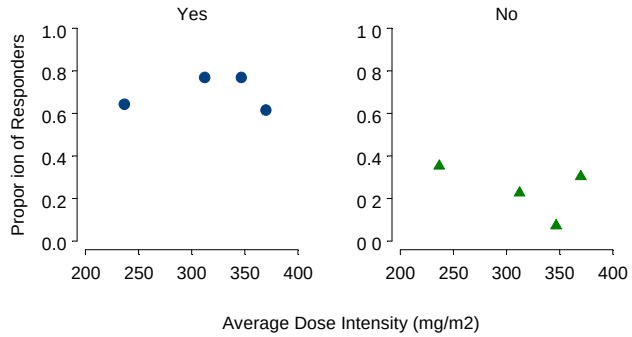

FIGURE 6: Hematologic Response vs. Average dose intensity (n=53)

Average dose received vs. Response

Average dose was calculated as the sum of all doses received during treatment in study divided by the number of days in study. For the complete and partial response analysis, as well as the hematological response analysis, the entire patient population was included (n=53) except for patient 731074. Patient 731074 did not have a record of average dose and therefore was excluded from the dose vs. response analysis. This patient was noted as having a complete hematological response, a partial cytogenetic response, and was classified as having a major cytogenetic response. Major/minor cytogenetic responses were only defined for patients in the PK subset therefore that analysis only includes those patients (n=33).

There is no significant difference between hematologic or cytogenetic response and average dose received (Figures 7, 8 and 9).

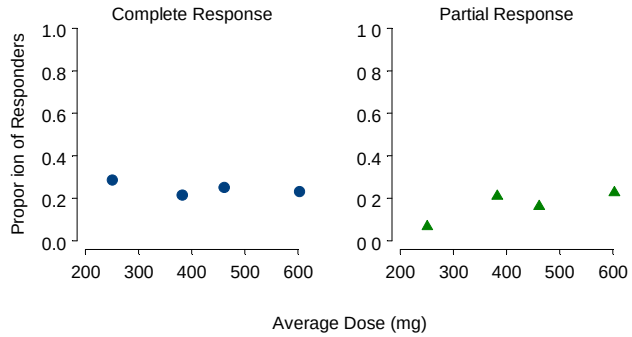

FIGURE 7: Complete, Partial Cytogenetic Response vs. Average Dose (n=53)

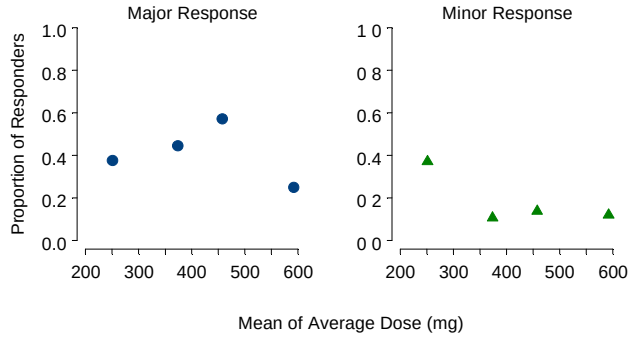

FIGURE 8: Major and Minor Cytogenetic Response vs. Average dose (n=33)

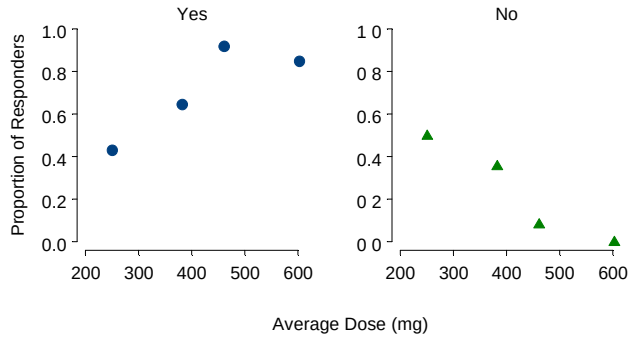

FIGURE 9: Hematologic Response vs. Average dose (n=53)

In summary, based on the limited data available, no significant correlation was seen between the $AUC_{0\text{-}24}$ of Gleevec and efficacy endpoints of hematological and/or cytogenetic response. In addition, no relationship was found between response and the total dose received or the average dose intensity.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Pharmacokinetic subset

Of the thirty-three patients with pharmacokinetic parameters 30 experienced at least one adverse

event. The most common adverse events seen in these patients were related to the blood and bone marrow (leukopenia, decreased hemoglobin, neutropenia, thrombocytopenia). Other common toxicities of muscle pain, nausea, vomiting and rash occurred in at least 40% of the pharmacokinetic subset of patients (see Table 3).

TABLE 3: Frequent Adverse events in the Pharmacokinetic subset (n=33)

Patients with AEs	**30 (90)**
Type	N (%)
Leukocytes (total WBC)	20 (67)
Hemoglobin (Hgb)	20 (67)
Neutrophils/granulocytes (ANC/AGC)	18 (60)
Platelets	16 (53)
Myalgia (muscle pain)	14 (47)
Nausea	13 (43)
Vomiting	12 (40)
Rash	11 (37)
Headache	10 (33)
Lymphopenia	10 (33)
Hypoglycemia	9 (30)
Hypocalcemia	9 (30)
Arthralgia	8 (27)
Abdominal pain or cramping	8 (27)
Hyperglycemia	8 (27)
Infection w/o neutropenia	8 (27)
Fatigue	8 (27)

Below are the exposure response graphs for the common hematological toxicities and the other toxicities occurring in at least 40% of the subject's. Since each subject could experience a toxicity multiple times during the study, the data was simplified to summarize the patients highest grade level for each toxicity. In addition, the data for AUC and Cmax were divided into quartiles and the mean of each quartile is plotted below. The symbols below represent the proportion of patients with grade 1/2 or grade 3/4 toxicities versus AUC or Cmax.

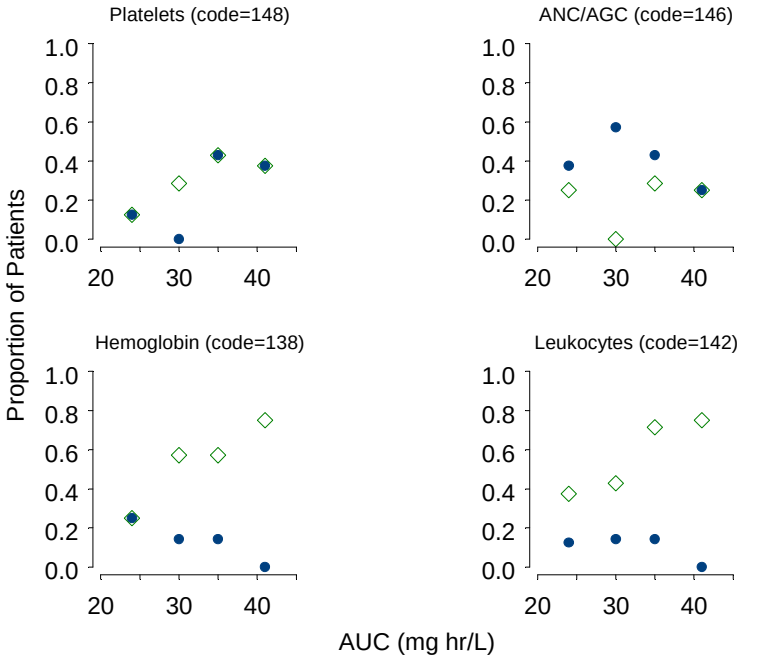

FIGURE 10: Proportion of patients with Grade 3/4 (closed circles) or Grade 1/2 (open triangles) hematological toxicities versus AUC

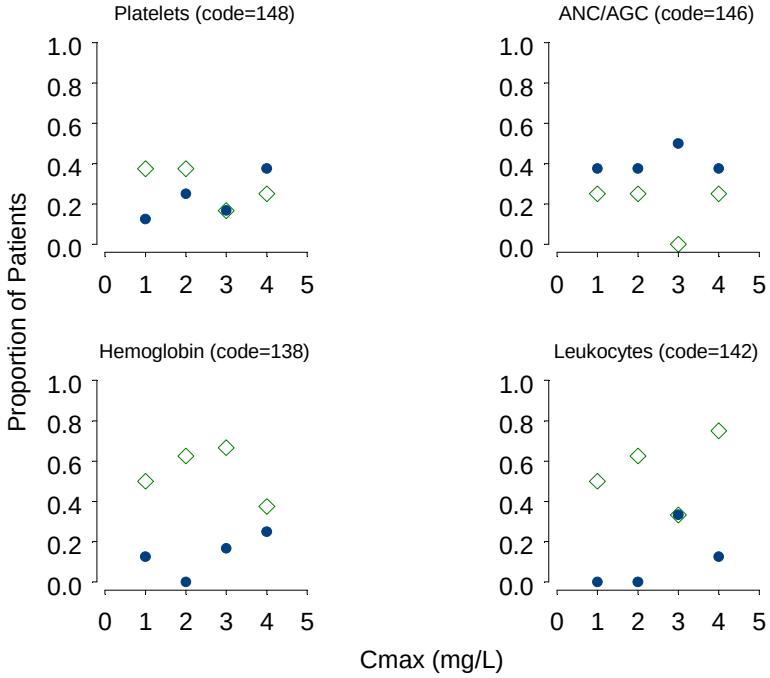

FIGURE 11: Proportion of patients with Grade 3/4 (closed circles) or Grade 1/2 (open triangles) hematologic toxicities versus Cmax.

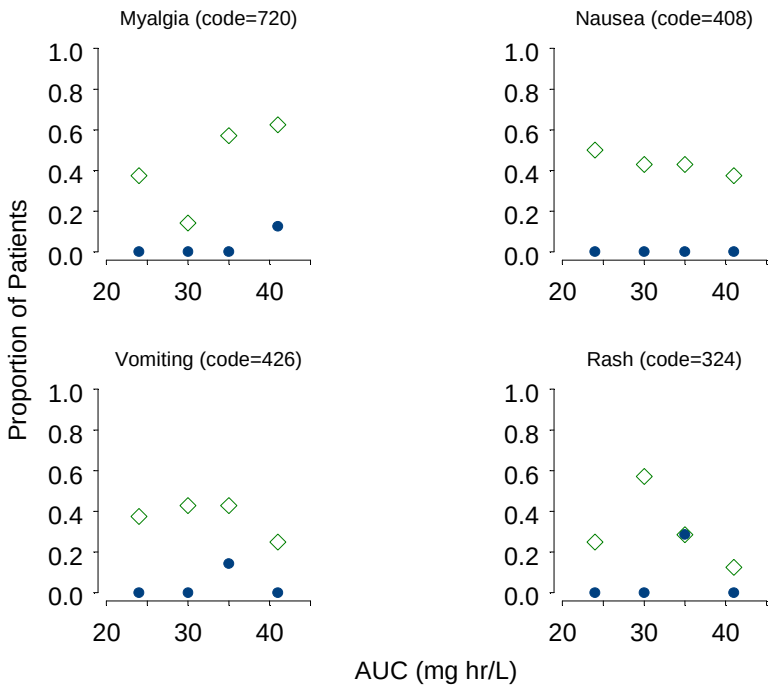

FIGURE 12: Proportion of patients with Grade 3/4 (closed circles) or Grade 1/2 (open triangles) toxicities (myalgia, nausea, vomiting, and rash) versus AUC.

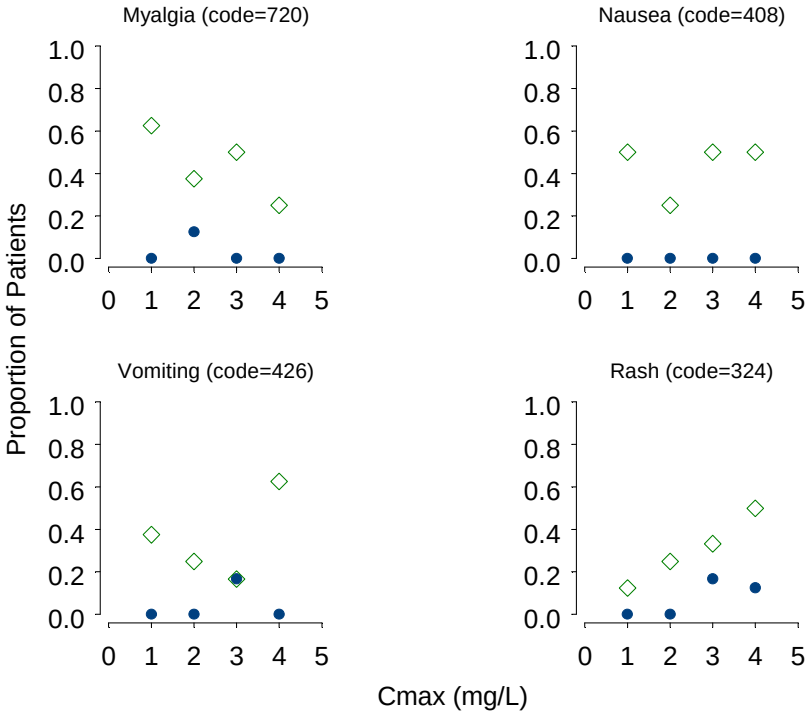

FIGURE 13: Proportion of patients with Grade 3/4 (closed circles) or Grade 1/2 (open triangles) toxicities (myalgia, nausea, vomiting, and rash) versus Average Dose Intensity

In summary, grade 3/4 toxicities were not as common in the pharmacokinetic subset as grade 1/2

toxicities. In general, the proportion of patients experiencing grade 1/2 toxicities increased as Cmax or AUC increased, however no statistical significance could be identified.

All patients

Out of the 54 patients who participated in study 2108, forty-seven experienced at least one adverse event (Table 4). Similar to the PK subpopulation, adverse events pertaining to the blood and bone marrow were the most frequent, followed by muscle pain.

TABLE 4: Frequent Adverse events in Study 2108

	Stratum 1 N=2	**Stratum 2 (N=1)**	**Stratum 3 N=51**
	n (%)	**n (%)**	**n (%)**
Patients with AEs	2 (100)	1(100)	44 (86.3)
Preferred term			
Hemoglobin		1 (100)	29 (56.9)
Neutrophils/granulocytes	1 (50)	1 (100)	26 (51.0)
Leukocytes	2 (100)	1 (100)	24 (47.1)
Platelets	1 (50)	1 (100)	21 (41.2)
Myalgia (muscle pain)			19 (37.3)
Nausea	1 (50)		18 (35.3)
Vomiting	1 (50)	1 (100)	16 (31.4)
Headache	1 (50)		15 (29.4)
Lymphopenia		1 (100)	12 (23.5)
Rash/desquamation	1 (50)		12 (23.5)
Abdominal pain or cramping	1 (50)		12 (23.5)
Arthralgia (joint pain)	1 (50)		12 (23.5)
Hypocalcemia			12 (23.5)
Hypoglycemia			11 (21.6)
Fatigue (lethargy, malaise,	1 (50)		10 (19.6)
asthenia)			
Hyperglycemia			10 (19.6)
Hypophosphatemia			10 (19.6)
Cough			10 (19.6)
Infection without	2 (100)		9 (17.6)
neutropenia			
Pain – other	1 (50)		9 (17.6)
Alkaline phosphatase			9 (17.6)
SGOT (AST)			9 (17.6)
SGPT (ALT)			9 (17.6)
Allergic rhinitis			8 (15.7)
Edema			7 (13.7)
Anorexia			7 (13.7)
Diarrhea (without colostomy)	1 (50)	1 (100)	7 (13.7)
Hypoalbuminemia			7 (13.7)
Hyponatremia			7 (13.7)
Transfusion: pRBCs*			6 (11.8)

	Stratum 1 N=2	Stratum 2 (N=1)	Stratum 3 N=51
	n (%)	n (%)	n (%)
Hypokalemia			6 (11.8)
Bone pain			6 (11.8)

Below are the exposure response graphs for the common hematological toxicities and the other toxicities occurring in at least 25% of the subjects. Since each subject could experience a toxicity multiple times during the study, the data was condensed to summarize the patients' worst response for each toxicity. In addition, the data for average dose intensity and average dose was divided into quartiles and the mean of each quartile is plotted below. The symbols below represent the proportion of patients with grade 1/2 or grade 3/4 toxicities versus average dose intensity or average dose.

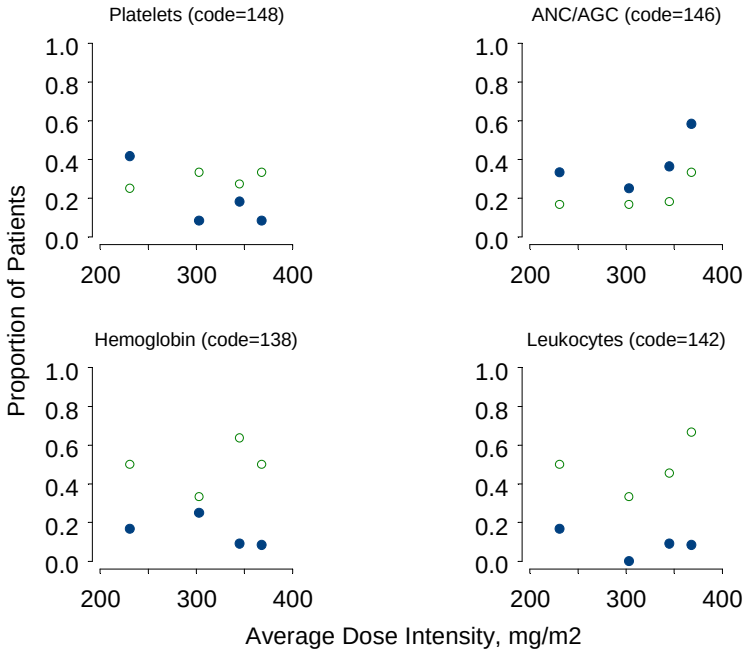

FIGURE 14: Proportion of patients with Grade 3/4 (closed circles) or Grade 1/2 (open circles) hematological toxicities versus Average Dose Intensity

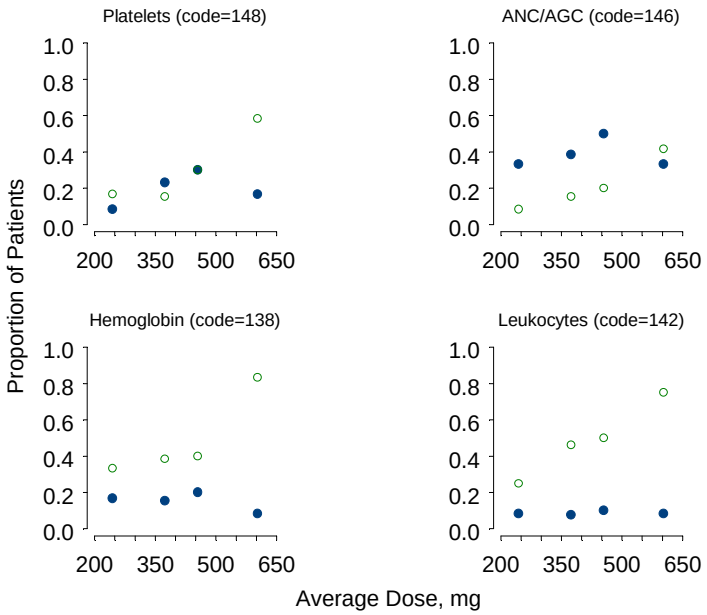

FIGURE 15: Proportion of patients with Grade 3/4 (closed circles) or Grade 1/2 (open circles) hematological toxicities versus Average Dose

In summary, grade 3/4 hematological toxicities were not as common as grade 1/2 toxicities except for neutropenia. In general, the proportion of patients experiencing grade 1/2 toxicities increased as average dose and average dose intensity increased.

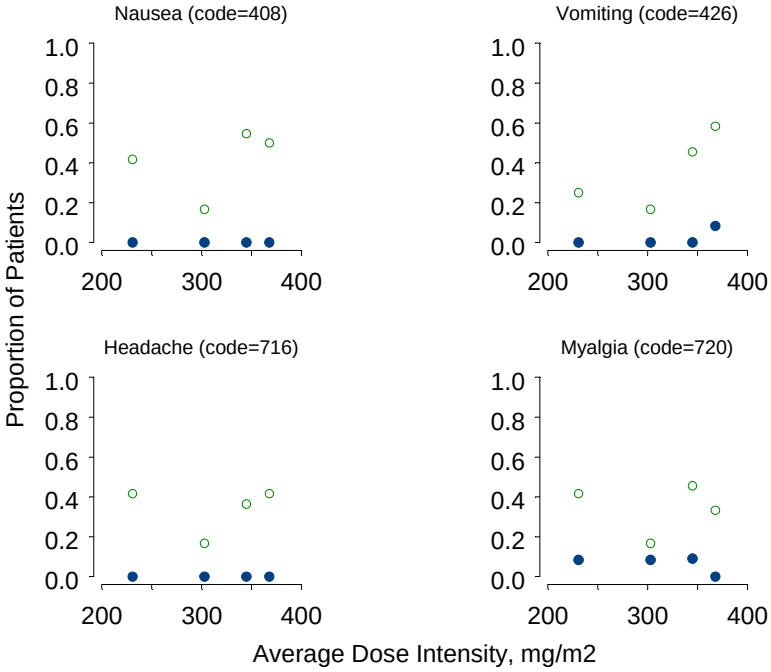

FIGURE 16: Proportion of patients with Grade 3/4 (closed circles) or Grade 1/2 (open circles) toxicities (Nausea, vomiting, headache and Myalgia) versus Average Dose Intensity

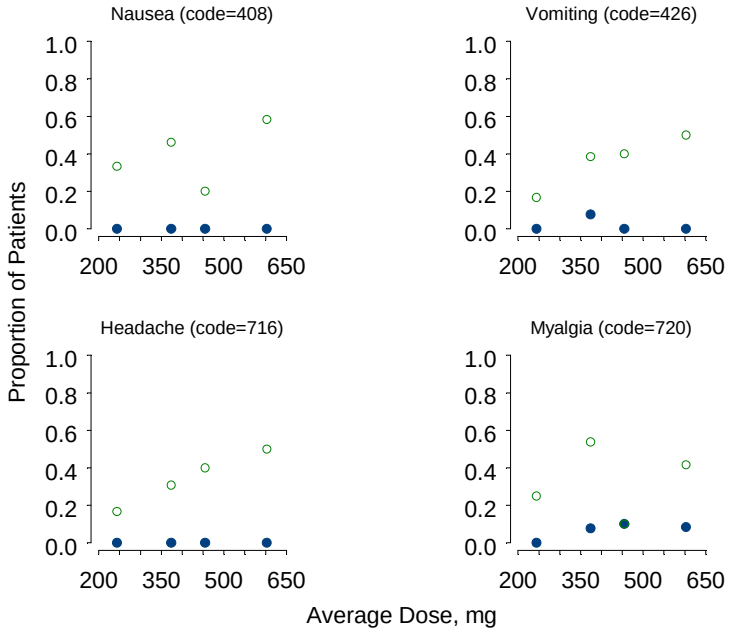

FIGURE 17: Proportion of patients with Grade 3/4 (closed circles) or Grade 1/2 (open circles) toxicities (Nausea, vomiting, headache and Myalgia) versus Average Dose.

Similar to the hematological toxicities grade 3/4 toxicities were not as common as grade 1/2 toxicities with regards to nausea, vomiting, headache and myalgia. In general, the proportion of patients experiencing grade 1/2 toxicities increased as average dose and average dose intensity increased.

2.2.4.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The 340 mg/m^2/day dose employed in Study 2108 proved to be acceptable based on efficacy and safety and its exposure similarity to the adult dose. Previous studies in adults show that the exposure (AUC_{0-24}) after a single dose of 400 mg and 600 mg is 24.8 and 39.7 µg hr/mL, respectively. The observed median AUC_{0-24} value for the pediatric study was 31.7 mg hr/L which lies within the range of the adult exposure suggesting that the dose selection of 340 mg/m^2 in pediatric patients is acceptable.

2.2.5 Pharmacokinetic Characteristics

What are the single dose and multiple dose PK parameters?

Single dose and multiple dose intensive pharmacokinetic profiles were taken in Study 0103 and were previously reviewed by Anne Zajicek, M.D., Pharm.D. (NDA 21-335/S-003). In this study, PK was determined on Day 1 and Day 8 in 27 pediatric patients who were being treated with escalating doses of imatinib (260, 340, 440, and 570 mg/m^2) administered once daily or twice daily. The majority of the patients received 260 mg/m^2 and 340 mg/m^2 daily and those results are summarized below in Table 5.

TABLE 5: Mean (SD) Day 1 and Day 8 PK parameters in children from Study 0103

Dose mg/m^2	N	Tmax (h)	Cmax (ng/mL)	Thalf (h)	AUC_{0-24} (ng h/mL)	$AUC_{0-\infty}$ (ng h/mL)	Vz/F (L)	Cl/F (L/h)
Day 1								
260	6	3.5	3624.5	8.9	50988.4	60582.7	118.9	8.9
		(2.5)	(1982.8)	(1.2)	(34873.2)	(39723.2)	(83.4)	(5.8)
340	8	3.7	2475.0	9.2	32113.6	39613.4	167.4	12.8
		(2.1)	(943.9)	(1.9)	(13097.1)	(17431.3)	(84.4)	(6.8)
Day 8								
260	6	3.3	3301.3	11.7	48611.0	67314.4	136.2	7.9
			(658.5)	(1.9)	(10407.2)	(18181.3)	(54.0)	(2.4)
340	8	2.3	4012.2	13.0	54982.8	80368.2	166.9	9.7
		(1.1)	(1535.4)	(3.7)	(26431.7)	(43872.1)	(74.7)	(5.3)

From this study it was concluded that the pharmacokinetics in pediatrics in adults are similar based on similar vales for clearance (pediatrics 6.38 L/hr/m^2, adult 5.78 L/hr/m^2).

In the current study (2108) sparse samples were collected between 1-3 hours, 6-9 hours and at 24 hours after drug intake on Day 1 in thirty-three patients who were dosed with Gleevec 340 mg/m^2 daily. A population PK model for data from study 2108 was constructed using characteristics from the three population PK models which have been published for studies 102, 106 and 109/110, all adult studies.

A one-compartment model with zero-order absorption and linear pharmacokinetics was used. Based on previous experience, Clearance and Volume are functions that may depend on covariates. The clearance model and the volume models for study 2108 used body weight (in kg), HGB, and WBC for covariates.

The model adequately characterized the pharmacokinetics in the 33 patients from study 2108 as Cmax and AUC for the 340 mg/m^2 dose are similar to those reported in study 0103 (see Table 5 and Table 6)

TABLE 6: Mean (SD) Day 1 model predicted PK for a 340 mg/m^2/day dose of Gleevec.

Dose (mg/m^2)	N	Cmax (mg/L)	AUC_{0-24} (mg h/L)
340	33	2.61	32.7
		(1.04)	(7.01)
Dose (mg)			
200	2	1.96	22.1
		(0.63)	(2.8)
300	6	3.40	27.4
		(1.08)	(3.2)
340	1	3.07	26.3
		(-)	(-)
400	7	2.55	32.5
		(0.72)	(5.26)
500	6	2.69	29.8
		(1.41)	(3.96)
600	8	2.16	38.2
		(1.02)	(5.4)
625	1	3.49	43.9

		(-)	(-)
700	2	2.025	43.1
		(0.12)	(0.59)

2.3 Intrinsic Factors

Gender and BSA were investigated for their impact on the exposure of Gleevec for the pharmacokinetic subset (Figures 18 and 19). As expected, significant ($p < 0.001$) correlations between BSA and exposure were seen as the dosing of Gleevec in this study was based on BSA. No significant findings between gender and exposure were identified.

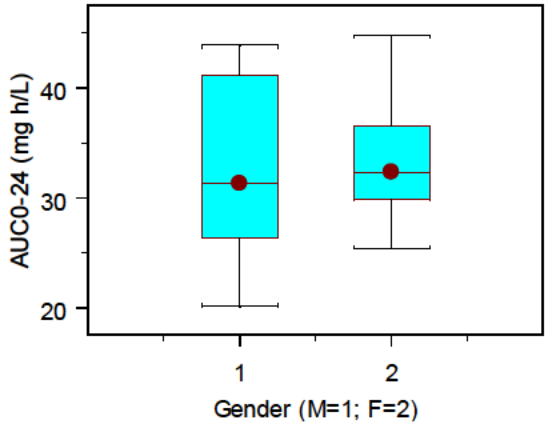

FIGURE 18: Exposure of Gleevec vs. Gender

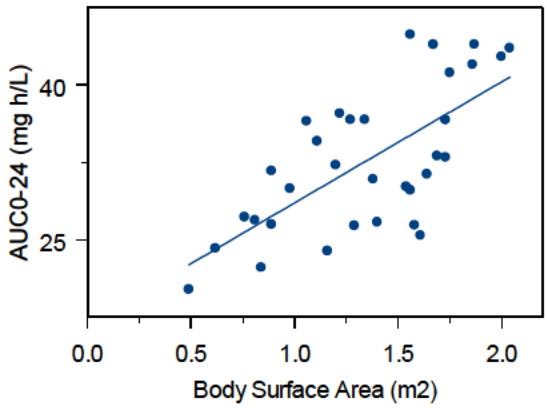

FIGURE 19: Exposure of Gleevec vs. BSA

2.4 Extrinsic Factors

No information regarding extrinsic factors and their influence on dose and exposure/response were provided in this study report.

3 Detailed Labeling Recommendations

Minor changes by the sponsor were proposed to the label pertaining to clinical pharmacology. The relevant clinical pharmacology sections are included below.

Highlights indicate information that the sponsor added, or ~~removed~~ from the current approved labeling. Double underlines indicate the content that was added by the agency and ~~strikethroughs~~ indicate content taken out by the agency.

Pharmacokinetics

The pharmacokinetics of Gleevec® (imatinib mesylate) have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib is well absorbed after oral administration with Cmax achieved within 2-4 hours post-dose. Mean absolute bioavailability is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative, are approximately 18 and 40 hours, respectively. Mean imatinib AUC increases proportionally with increasing doses ranging from 25 mg-1,000 mg. There is no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5- to 2.5-fold at steady state when Gleevec is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and α1-acid glycoprotein.

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

Metabolism and Elimination

CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows *in vitro* potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for imatinib. The plasma protein binding of the N-demethylated metabolite CGP71588 is similar to that of the parent compound.

Elimination is predominately in the feces, mostly as metabolites. Based on the recovery of compound(s) after an oral 14C-labeled 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.

Typically, clearance of imatinib in a 50-year-old patient weighing 50 kg is expected to be 8 L/h, while for a 50-year-old patient weighing 100 kg the clearance will increase to 14 L/h. However, the inter-patient variability of 40% in clearance does not warrant initial dose adjustment based on body weight and/or age but indicates the need for close monitoring for treatment-related toxicity.

Special Populations

Pediatric: As in adult patients, imatinib was rapidly absorbed after oral administration in

pediatric patients, with a Cmax of 2-4 hours. Apparent oral clearance was similar to adult values (11.0 L/hr/m2 in children vs. 10.0 L/hr/m2 in adults), as was the half-life (14.8 hours in children vs. 17.1 hours in adults). Dosing in children at both 260 mg/m2 and 340 mg/m2 achieved an AUC similar to the 400-mg dose in adults. The comparison of AUC(0-24) on Day 8 vs. Day 1 at 260 mg/m2 and 340 mg/m2 dose levels revealed a 1.5- and 2.2-fold drug accumulation, respectively, after repeated once-daily dosing. Mean imatinib AUC did not increase proportionally with increasing dose.

Hepatic Insufficiency: The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 84 cancer patients with varying degrees of hepatic impairment (Table 1) at imatinib doses ranging from 100-800 mg. Exposure to both imatinib and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired groups and the normal group. However, patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady state, the mean Cmax/dose and AUC24/dose for imatinib increased by about 63% and 45%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. The mean Cmax/dose and AUC24/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Table 1: Liver Function Classification

Liver Function Test	Normal (n=14)	Mild (n=30)	Moderate (n=20)	Severe (n=20)
Total Bilirubin	≤ ULN	1.5 ULN	>1.5-3x ULN	>3-10x ULN
SGOT	≤ ULN	> ULN (can be normal if Total Bilirubin is >ULN)	Any	Any

ULN=upper limit of normal for the institution

Renal Insufficiency: No clinical studies were conducted with Gleevec in patients with decreased renal function (studies excluded patients with serum creatinine concentration more than 2 times the upper limit of the normal range). Imatinib and its metabolites are not significantly excreted via the kidney.

Drug-Drug Interactions

CYP3A4 Inhibitors: There was a significant increase in exposure to imatinib (mean Cmax and AUC increased by 26% and 40%, respectively) in healthy subjects when Gleevec was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). (See PRECAUTIONS.)

CYP3A4 Substrates: Gleevec increased the mean Cmax and AUC of simvastatin (CYP3A4 substrate) by 2- and 3.5-fold, respectively, indicating an inhibition of CYP3A4 by Gleevec. (See PRECAUTIONS.)

CYP3A4 Inducers: Pretreatment of 14 healthy volunteers with multiple doses of

rifampin, 600 mg daily for 8 days, followed by a single 400-mg dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold (90% confidence interval = 3.5- to 4.3-fold), which represents mean decreases in Cmax, AUC(0-24) and AUC(0-∞) by 54%, 68% and 74%, of the respective values without rifampin treatment. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

In Vitro Studies of CYP Enzyme Inhibition: Human liver microsome studies demonstrated that Gleevec is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with Ki values of 27, 7.5 and 8 μM, respectively. Gleevec is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5. (See PRECAUTIONS.)

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PRECAUTIONS

Drug Interactions

Drugs that May Alter Imatinib Plasma Concentrations

Drugs that may **increase** imatinib plasma concentrations:

Caution is recommended when administering Gleevec with inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin). Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib when Gleevec is coadministered with ketoconazole (CYP3A4 inhibitor).

Drugs that may **decrease** imatinib plasma concentrations:

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or St. John's Wort) may significantly reduce exposure to Gleevec. Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold, which significantly ($p<0.05$) decreased mean Cmax and AUC(0-∞). In patients where rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Drugs that May Have their Plasma Concentration Altered by Gleevec

Gleevec increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Gleevec. Particular caution is recommended when administering Gleevec with CYP3A4 substrates that have a narrow therapeutic window (e.g., cyclosporine or pimozide). Gleevec will increase plasma concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.).

Because *warfarin* is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low-molecular weight or standard heparin.

In vitro, Gleevec inhibits the cytochrome P450 isoenzyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is expected to be increased when coadministered with Gleevec. No specific studies have been performed and caution is recommended.

In vitro, Gleevec inhibits acetaminophen O-glucuronidation (Ki value of 58.5 μM) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when coadministered with Gleevec. No specific studies in humans have been performed and caution is recommended.

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DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with chronic myeloid leukemia or gastrointestinal stromal tumors.

The recommended dosage of Gleevec® (imatinib mesylate) is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. The recommended dosage of Gleevec for children with newly diagnosed Ph+ CML is 340mg/m^2/day (not to exceed 600mg). The recommended Gleevec dosage is 260 mg/m2/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy. The recommended dosage of Gleevec is 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST.

The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

In children, Gleevec treatment can be given as a once-daily dose or alternatively the daily dose may be split into two - once in the morning and once in the evening. There is no experience with Gleevec treatment in children under 2 (b)(4) years of age.

Patients with mild and moderate hepatic impairment should be treated at a starting dose of 400 mg/day. Patients with severe hepatic impairment should be treated at a starting dose of 300 mg/day. (See CLINICAL PHARMACOLOGY and PRECAUTIONS)

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 mL for a 100-mg tablet, and 200 mL for a 400-mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the

following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6-12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response. In children with chronic phase CML, daily doses can be increased under circumstances similar to those leading to an increase in adult chronic phase disease, from 260 mg/m2/day to 340 mg/m2/day, as clinically indicated.

Dosage of Gleevec should be increased by at least 50%, and clinical response should be carefully monitored, in patients receiving Gleevec with a potent CYP3A4 inducer such as rifampin or phenytoin.

For daily dosing of 800 mg and above, dosing should be accomplished using the 400-mg tablet to reduce exposure to iron.

4 Appendices

4.1 Referenced reviews

4.1.1 Original NDA 21-335 - CML

Submitted on Feb 27, 2001, April 10, 2001 and April 12, 2001. Review completed and posted by John Duan, Ph.D. in DFS.

4.1.2 sNDA 21-335 - GIST

Submitted on Oct 15, 2001 and Dec 7, 2001. Review completed and posted by Gene Williams, PhD. in DFS

4.1.3 sNDA NDA 21-335 - Pediatric CML

Submitted on June 28, 2002. Review completed and posted by Anne Zajicek, M.D., Pharm.D. in DFS

4.1.4 Original NDA 21-588 switch from capsules to tablets

Submitted on December 13, 2002. Review completed and posted by Anne Zajicek, M.D., Pharm.D. in DFS

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