CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21-335

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#:	21-335
Applicant:	Novartis Pharmaceuticals Corporation
Name of Drug:	Gleevec (STI-571; imatinib mesylate) capsules
Indications:	Interferon-refractory/intolerant chronic myeloid leukemia (CML), Philadelphia (Ph) chromosome-positive chronic myeloid in myeloid blast crisis, Ph chromosome-positive CML in accelerated phase, relapsed/refractory CML in lymphoid blast crisis and relapsed/refractory adults with Ph chromosome-positive acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML).
Documents Reviewed:	Volumes 1.1, 1.50, 1.55, 1.56, 1.59, 1.60, 1.63, 1.67 and 1.72
Medical Officer:	Martin Cohen, M.D.
Statistical Reviewer:	Mark Rothmann, Ph. D.

1. BACKGROUND, OVERVIEW AND EFFICACY SUMMARY

In support of Gleevec Capsules as treatment for patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy, the sponsor submitted an NDA that consists of five clinical studies. This review will concentrate on studies 102, 109 and 110.

Gleevec is a protein-tyrosine kinase inhibitor, a specific inhibitor of Bcr-Abl tyrosine kinase.

The hematologic and cytogenetic response rates for studies 102, 109 and 110 are summarized in Reviewer's Table 1 below.

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Reviewer's Table 1. Hematologic and Cytogenetic Responses for Patients with CML only (ITT Population [1])

Endpoint	Study 102	Study 109	Study 110
Hematological Response			
Rate	68/260 (26%)	148/235 (63%)	468/532 (88%)
95% CI	(20.9%, 31.9%)	(56.5%, 69.2%)	(84.9%, 90.6%)
Complete Hematological Response: Rate	10/260 (4%)	66/235 (28%)	468/532 (88%)
95% CI	(1.9%, 7.0%)	(22.4%, 34.3%)	(84.9%, 90.6%)
No evidence of leukemia			
Rate	8/260 (3%)	26/235 (11%)	
95% CI	(1.3%, 6.0%)	(7.4%, 15.8%)	
Return to chronic phase			
Rate	50/260 (19%)	56/235 (24%)	
95% CI	(14.6%, 24.6%)	(18.5%, 29.8%)	
Major Cytogenetic Response [2]			
Rate	35/260 (13%)	50/235 (21%)	263/532 (49%)
95% CI	(9.6%, 18.2%)	(16.2%, 27.1%)	(45.1%, 53.8%)
Complete Cytogenetic Response [2]			
Rate	13/260 (5%)	34/235 (14%)	160/532 (30%)
95% CI	(2.7%, 8.4%)	(10.2%, 19.6%)	(26.2%, 34.2%)

[1] All enrolled patients received at least one dose of study medication. These patients form the intent-to-treat (ITT) patient population.

[2] Values are for unconfirmed cytogenetic responses.

2. STATISTICAL ISSUES

- For studies 102 and 109, since there was no randomization of patients to initial dose of Gleevec (400 mg daily and 600 mg daily), formal comparisons of the results by initial dose group are inappropriate. Differences in the results of the two initial dose groups may be due to patient demographic differences between the two initial dose groups – for example, for study 102 the median time from first diagnosis of blast crisis to study entry is 2.3 months for the 400 mg daily initial dose group compared to 0.5 months for the 600 mg daily initial dose group (for study 109, the median time from first diagnosis to study entry is 1.4 months for the 400 mg daily initial dose group compared to 0.8 months for the 600 mg daily initial dose group).

- Some patients with hematological responses who relapsed (see FDA medical officer's review) had missing response assessments prior to relapse. The corresponding

durations of response should be regarded as interval censored. The sponsor regarded these observations as events with durations up to the observed time of relapse. The FDA medical officer regarded these observations as censored at the time to the last uninterrupted scheduled visit (this can have any effect on the Kaplan-Meier curves, estimates of medians or any other percentiles).

3. BRIEF DESCRIPTION OF STUDIES

Study 102

Study 102 is a phase II, open-label, non-randomized, multicenter study of patients with either untreated or previously treated for myeloid blast crisis. According to the protocol, during part I of the study, patients will receive daily one oral administration of Gleevec at a dose of 400 mg for 24 weeks with appropriate dose reductions due to toxicity. After which time a patient may be eligible to receive additional therapy during Part 2 of the study provided the investigator believes that there are signs of benefit from the treatment with Gleevec and in the absence of safety concerns. Additional therapy will continue on a daily basis until either death, the development of intolerable toxicity or until the investigator feels it is no longer in the best interest of the patient. The number of visits will be less frequent during part 2. Those patients who discontinue treatment will be followed indefinitely for survival.

For patients enrolled between Amendment 1 (dated October 6, 1999) and Amendment 2 (dated December 21, 1999), the initial dose of Gleevec could be increased 600 mg once daily at the discretion of the investigator or sponsor. Patients enrolled after Amendment 2 received an initial dose of Gleevec of 600 mg once daily.

A total of 260 were enrolled into this study – thirty-seven receiving an initial dose of 400 mg once daily of Gleevec and 223 receiving an initial dose of 600 mg once daily of Gleevec. One hundred sixty-five (165) patients had been untreated for myeloid blast crisis, while 95 patients were treated previously for myeloid blast crisis.

Efficacy assessments and statistical analysis plan: All enrolled patients received at least one dose of study medication. These patients form the intent-to-treat (ITT) patient population. The ***primary efficacy endpoint*** is confirmed overall hematological response. Assessments were categorized as complete hematological response, no evidence of leukemia, return to chronic phase, no response, progression, death, or not assessable. The first three of these categories were regarded as a hematological response and were assigned only if the response was confirmed by an evaluation showing a similar or better assessment at least four weeks later (without any intermediary value of "no response" or progression). Analyses will be based on a 95% confidence interval for the response rate. Such analysis will be performed on the ITT overall population and by group - a no prior therapy for blast crisis group and a previous therapy for blast crisis group. Patients that drop out without having a hematological response will be considered non-responders as

well as those patients who drop out after showing a hematological response but were not observed for at least four weeks.

For untreated patients, the sample size was based on Fleming's single-stage design where the probability of rejecting the null hypothesis of a true response rate of at most 15% is at most 2.5% if the null hypothesis is true and the probability of rejecting the alternative hypothesis of a true response rate of at least 30% is at most 10%, if the alternative hypothesis is true. A sample size of 79 patients is sufficient to meet these requirements. To account for dropouts, the planned sample size was increased to 100 untreated patients.

Secondary efficacy endpoints include: Time to (confirmed) hematological response, duration of (confirmed) hematological response, time to progression, time to major cytogenetic response, duration of cytogenetic response, overall survival, cancer related symptoms and ECOG performance status.

Sponsor's Table 1 gives the overall hemalogotic response rates and hematologic response rates for the untreated and previously treated for myeloid blast crisis subgroups.

Sponsor's Table 1. Number (%) of Patients with a Hematologic Response (Confirmed) (ITT Population)

	Disease Group		
Endpoint	**Untreated N=165**	**Treated N=95**	**Total N=260**
Hematological Response			
Rate	**50 (30.3%)**	**18 (18.9%)**	**68 (26.2%)**
95% CI	**(23.4%-37.9%)**	**(11.6%, 28.3%)**	**(20.9%, 31.9%)**
Complete hem. remission	7 (4.2%)	3 (3.2%)	10 (3.8%)
No evidence of leukemia	7 (4.2%)	1 (1.1%)	8 (3.1%)
Return to chronic phase	36 (21.8%)	14 (14.7%)	50 (19.2%)
Absence of Response	**96 (58.1%)**	**66 (69.5%)**	**162 (62.3%)**
No response[1]	50 (30.3%)	34 (35.8%)	84 (32.2%)
Progression without response	37 (22.4%)	29 (30.5%)	66 (25.4%)
Death without response	9 (5.5%)	3 (3.2%)	12 (4.6%)
Not assessable[2]	**19 (11.5%)**	**11 (11.6%)**	**30 (11.5%)**

[1] Values available to indicate absence of response

[2] Not done, or values available not allowing determination of presence or absence of response and its confirmation.

The 95% confidence interval for hematologic response rate for the untreated patient group lies entirely above 15%.

Study 109

Study 109 is a phase II, open-label, non-randomized, multicenter study of patients with accelerated phase. According to the original protocol (dated June 28, 1999), patients received daily one oral administration of Gleevec at a dose of 400 mg for 24 weeks with appropriate dose reductions due to toxicity. For patients enrolled after Amendment 1 (dated October 5, 1999), the initial dose of Gleevec was increased to 600 mg once daily. After which time a patient may be eligible to receive additional therapy during Part 2 of the study provided the investigator believes that there are signs of benefit from the treatment with Gleevec and in the absence of safety concerns. Additional therapy will continue on a daily basis until either death, the development of intolerable toxicity or until the investigator feels it is no longer in the best interest of the patient. The number of visits will be less frequent during part 2. Those patients who discontinue treatment will be followed indefinitely for survival.

A total of 235 patients were enrolled into this study – seventy-seven receiving an initial dose of 400 mg once daily of Gleevec and 158 receiving an initial dose of 600 mg once daily of Gleevec.

Efficacy assessments and statistical analysis plan: All enrolled patients received at least one dose of study medication. These patients form the intent-to-treat (ITT) patient population. The ***primary efficacy endpoint*** is confirmed overall hematological response. Assessments were categorized as complete hematological response, no evidence of leukemia, return to chronic phase, no response, progression, death, or not assessable. The first three of these categories were regarded as a hematological response and were assigned only if the response was confirmed by an evaluation showing a similar or better assessment at least four weeks later (without any intermediary value of "no response" or progression). Analyses will be based on a 95% confidence interval for the response rate. Such analysis will be performed on the ITT overall population and by group - a no prior therapy for blast crisis group and a previous therapy for blast crisis group. Patients that drop out without having a hematological response will be considered non-responders as well as those patients who drop out after showing a hematological response but were not observed for at least four weeks.

The sponsor would consider Gleevec active for this study if there were at least 29 responders out of a planned recruitment of 68 patients. This criteria requires that the 95% CI for confirmed hematological response lies entirely above 30%.

Secondary efficacy endpoints include: time to (confirmed) hematological response, duration of (confirmed) hematological response, major cytogenetic respones, time to progression and overall survival. Other secondary endpoints include: time to blast crisis, time to major cytogenetic response, duration of major cytogenetic response, cancer related symptoms and ECOG Performance Status.

The sample size was based on Fleming's single-stage design where the probability of rejecting the null hypothesis of a true response rate of at most 30% is at most 2.5% if the null hypothesis is true and the probability of rejecting the alternative hypothesis of a true response rate of at least 50% is at most 10%, if the alternative hypothesis is true. A sample size of 68 patients is sufficient to meet these requirements.

Sponsor's Table 2 gives the overall hemalogotic response rates.

Sponsor's Table 2. Number (%) of CML AP Patients with a Hematologic Response (Confirmed) (ITT Population)

Endpoint	All Initial Doses N=235
Hematological Response	
Rate	**148 (63.0%)**
95% CI	**(56.5% - 69.2%)**
Complete hem. remission	65 (27.7%)
No evidence of leukemia	27 (11.5%)
Return to chronic phase	56 (23.8%)
Absence of Response	
No response	38 (16.2%)
Progression without response	24 (10.2%)
Death without response	3 (1.3%)
Not assessable[1]	**22 (9.4%)**

[1] Not assessable was assigned to patients who only had 1 post-baseline assessment and did not discontinue due to AE or lab abnormality (classed as progression) or death.

The 95% confidence interval for hematologic response rate lies entirely above 30%.

Study 110

Study 110 is a phase II, open-label, non-randomized, multicenter study in patients with chronic myeloid leukemia who are refractory to or intolerant of interferon-alpha (IFN). During the main part of this study, patients will receive daily one oral administration of Gleevec at a dose of 400 mg, for up to 12 months. After which time a patient may be eligible to receive additional therapy provided the investigator believes that there are signs of benefit from the treatment with Gleevec and in the absence of safety concerns. The number of visits will be less frequent during this second part. Those patients who discontinue treatment will be followed for survival.

A total of 532 patients were enrolled into this study – 152 had hematologic failures, 186 had cytogenic failures and 194 were IFN intolerant. Except for eight patients from two centers (one in Germany and one in Italy) who were treated with a beginning dose of 600 mg daily, all patients were initially treated at 400 mg daily.

Efficacy assessments and statistical analysis plan: All enrolled patients received at least one dose of study medication. These patients form the intent-to-treat (ITT) patient population. The ***primary efficacy endpoints*** are complete and major cytogenetic response. Based on the percentage of positive cells at each bone marrow assessment, a cytogenetic response was categorized as complete (0% Ph+ cells), partial (>0-35% Ph+ cells), minor (>35-65% Ph+ cells), minimal (>65-95% Ph+ cells), none (>95% Ph+ cells), not done (< 20 metaphases were examined and/or response could not be assigned) and Ph negative at baseline. The first two categories (complete + partial) defined a major cytogenetic response. According to the sponsor most patients had either one or two total bone marrow assessments. Because of this, analyses were primarily based on unconfirmed responses. Analyses will be based on a 95% confidence interval for the response rate.

The sponsor's success criterion for patients with hematologic failures is at least 21 responders out of a planned recruitment of 132 patients. This criteria requires that the 95% CI for major cytogenetic response lies entirely above 10%. The sponsor's success criterion for patients with cytogenetic failures is at least 19 responders out of a planned recruitment of 79 patients. This criteria requires that the 95% CI for major cytogenetic response lies entirely above 15%.

Hematological response assessments were categorized as complete hematological response, no response, progression, death, or not assessable. A complete hematological response was assigned only if the response was confirmed at least four weeks later (without any intermediary value of "no response" or progression).

Secondary efficacy endpoints include: rate and duration of complete hematological response, time to (confirmed) hematological response, duration of complete cytogenetic response and major cytogenetic response, major cytogenetic respones, time to blast crisis, rate and duration of hematological and cytogenetic response in patients intolerable of IFN, and overall survival.

Sample sizes were based on Fleming's single-stage design. For hematologic failures, the sample size was based on an at most 2.5% probability of rejecting the null hypothesis of a true response rate of at most 10% when the null hypothesis is true and an at most 10% probability of rejecting the alternative hypothesis of a true response rate of at least 20% when the alternative hypothesis is true. A sample size of 132 patients is sufficient to meet these requirements. For cytogenetic failures, the sample size was based on an at most 2.5% probability of rejecting the null hypothesis of a true response rate of at most 15% when the null hypothesis is true and an at most 10% probability of rejecting the alternative hypothesis of a true response rate of at least 30% when the alternative hypothesis is true. A sample size of 79 patients is sufficient to meet these requirements.

Sponsor's Tables 3a and 3b give, respectively, the unconfirmed and confirmed major cytogenetic response rates overall and for the hematological failures, cytogenetic failures and INF intolerant at baseline subgroups.

Sponsor's Table 3a. Unconfirmed Cytogenetic Responses – Overall and for Disease Subgroups Defined at Baseline (ITT Population)

Endpoint	N (%)	95% CI
Overall (N = 532)		
Major (CR + PR)	**263 (49.4%)**	**(45.1%, 53.8%)**
Complete (CR)	160 (30.1%)	(26.2%, 34.2%)
Partial (PR)	103 (19.4%)	(16.1%, 23.0%)
Minor	30 (5.6%)	
Minimal	63 (11.8%)	
None	121 (22.7%)	
Not done	50 (9.4%)	
Progression	3 (0.6%)	
Ph neg. at baseline	2 (0.4%)	
Hematological Failures (N = 152)		
Major (CR + PR)	**55 (36.2%)**	**(28.6%, 44.4%)**
Complete	31 (20.4%)	(14.3%, 27.7%)
Partial	24 (15.8%)	(10.4%, 22.6%)
Minor	8 (5.3%)	
Minimal	23 (15.1%)	
None	41 (27.0%)	
Not done	21 (13.8%)	
Progression	2 (1.3%)	
Ph neg. at baseline	2 (1.3%)	
Cytogenetic Failures (N = 186)		
Major (CR + PR)	**95 (51.1%)**	**(43.7%, 58.5%)**
Complete	56 (30.1%)	(23.6%, 37.2%)
Partial	39 (21.0%)	(15.4%, 27.5%)
Minor	15 (8.1%)	
Minimal	21 (11.3%)	
None	38 (20.4%)	
Not done	16 (8.6%)	
Progression	1 (0.5%)	
Ph neg. at baseline	0	
INF Intolerant (N = 194)		
Major (CR + PR)	**113 (58.2%)**	**(51.0%, 65.3%)**
Complete	73 (37.6%)	(30.8%, 44.9%)
Partial	40 (20.6%)	(15.2%, 27.0%)
Minor	7 (3.6%)	
Minimal	19 (9.8%)	
None	42 (21.6%)	
Not done	13 (6.7%)	
Progression	0	

Ph neg. at baseline	0

Those confirmed major cytogenetic response rates are given in the below table.

Sponsor's Table 3b. Confirmed Cytogenetic Responses – Overall and for Disease Subgroups Defined at Baseline (ITT Population)

Endpoint	N (%)	95% CI
Overall (N = 532)		
Major (CR + PR)	**202 (38.0%)**	**(33.8%, 42.2%)**
Complete (CR)	78 (14.7%)	(11.8%, 18.0%)
Partial (PR)	124 (23.3%)	(19.8%, 27.1%)
Minor	32 (6.0%)	
Minimal	38 (7.1%)	
None	111 (20.9%)	
Not done	135 (25.4%)	
Progression	12 (2.3%)	
Ph neg. at baseline	2 (0.4%)	
Hematological Failures (N = 152)		
Major (CR + PR)	**33 (21.7%)**	**(15.4%, 29.1%)**
Complete	8 (5.3%)	(2.3%, 10.1%)
Partial	25 (16.4%)	(10.9%, 23.3%)
Minor	8 (5.3%)	
Minimal	10 (6.6%)	
None	34 (22.4%)	
Not done	61 (40.1%)	
Progression	4 (2.6%)	
Ph neg. at baseline	2 (1.3%)	
Cytogenetic Failures (N = 186)		
Major (CR + PR)	**76 (40.9%)**	**(33.7%, 48.3%)**
Complete	29 (15.6%)	(10.7%, 21.6%)
Partial	47 (25.3%)	(19.2%, 32.1%)
Minor	14 (7.5%)	
Minimal	15 (8.1%)	
None	39 (21.0%)	
Not done	40 (21.5%)	
Progression	2 (1.1%)	
Ph neg. at baseline	0	

INF Intolerant (N = 194)		
Major (CR + PR)	**93 (47.9%)**	**(40.7%, 55.2%)**
Complete	41 (21.1%)	(15.6%, 27.6%)
Partial	52 (26.8%)	(20.7%, 33.6%)
Minor	10 (5.2%)	
Minimal	13 (6.7%)	
None	38 (19.6%)	
Not done	34 (17.5%)	
Progression	6 (3.1%)	
Ph neg. at baseline	0	

For each confirmed or unconfirmed cytogenetic response, the 95% confidence interval for the major cytogenetic response rate for the hematologic failure subgroup lies entirely above 10% and the 95% confidence interval for the major cytogenetic response rate for the cytogenetic failure subgroup lies entirely above 15%.

Sponsor's Table 4 gives the overall hematologic response rates and hematologic response rates for the hematological failures, cytogenetic failures and INF intolerant subgroups.

Sponsor's Table 4. Hematolgical Response Rates (Confirmed) - Overall and for Disease Subgroups Defined at Baseline (ITT Population)

Endpoint	N (%)	95% CI
Overall (N = 532)		
Complete hem. remission	468 (88.0%)	(84.9%, 90.6%)
No response	54 (10.2%)	
Not assessable	10 (1.9%)	
Hematological Failures (N = 152)		
Complete hem. remission	126 (82.9%)	(76.0%, 88.5%)
No response	22 (14.5%)	
Not assessable	4 (2.6%)	
Cytogenetic Failures (N = 186)		
Complete hem. remission	173 (93.0%)	(88.3%, 96.2%)
No response	12 (6.5%)	
Not assessable	1 (0.5%)	
INF Intolerant (N = 194)		
Complete hem. remission	169 (87.1%)	(81.6%, 91.5%)
No response	20 (10.3%)	
Not assessable	5 (2.6%)	

4. SUMMARY AND CONCLUSIONS

The hematologic and cytogenetic response rates for studies 102, 109 and 110 are summarized in Reviewer's Table 1 below.

Reviewer's Table 1. Hematologic and Cytogenetic Responses for Patients with CML only (ITT Population [1])

Endpoint	Study 102	Study 109	Study 110
Hematological Response			
Rate	68/260 (26%)	148/235 (63%)	468/532 (88%)
95% CI	(20.9%, 31.9%)	(56.5%, 69.2%)	(84.9%, 90.6%)
Complete Hematological Response: Rate	10/260 (4%)	66/235 (28%)	468/532 (88%)
95% CI	(1.9%, 7.0%)	(22.4%, 34.3%)	(84.9%, 90.6%)
No evidence of leukemia			
Rate	8/260 (3%)	26/235 (11%)	
95% CI	(1.3%, 6.0%)	(7.4%, 15.8%)	
Return to chronic phase			
Rate	50/260 (19%)	56/235 (24%)	
95% CI	(14.6%, 24.6%)	(18.5%, 29.8%)	
Major Cytogenetic Response [2]			
Rate	35/260 (13%)	50/235 (21%)	263/532 (49%)
95% CI	(9.6%, 18.2%)	(16.2%, 27.1%)	(45.1%, 53.8%)
Complete Cytogenetic Response [2]			
Rate	13/260 (5%)	34/235 (14%)	160/532 (30%)
95% CI	(2.7%, 8.4%)	(10.2%, 19.6%)	(26.2%, 34.2%)

[1] All enrolled patients received at least one dose of study medication. These patients form the intent-to-treat (ITT) patient population.
[2] Values are for unconfirmed cytogenetic responses.

Conclusions: Results of one-armed studies are exploratory. Conclusions should be based on clinical judgement.

/S/

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