CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number #:	NDA 203-585 / 000
Supplement #:	Original New Drug Application
Drug Name:	Omacetaxine mepeseccinate for injection at 3.5 mg/vial
Indication(s):	Treatment of adult patients with chronic or accelerate phase chronic myelogeneous leukemia (CML) with resistance and/or intolerance to prior tyrosine kinase inhibitor (TKI) therapy including imatinib, dasatinib or nilotinib
Applicant:	Cephalon, Inc.
Date(s):	Submission date: 30 March 2012 PDUFA date: 30 September 2012 Review completion date: 31 August 2012
Review Priority:	Priority review
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Chia-Wen Ko, Ph.D.
Concurring Reviewers:	Mark Rothmann, Ph.D., Team Leader Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Division of Hematology Products
Clinical Team:	Firoozeh Alvandi, M.D. (Primary reviewer) Virginia Kwitkowski, M.D. (Medical team leader)
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Keywords: CML, single-arm study, response rate, onset and duration of response

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1 EXECUTIVE SUMMARY

This application is seeking an indication for omacetaxine as the treatment of adult patients with chronic or accelerated phase chronic myelogeneous leukemia (CML) with resistance and/or intolerance to prior tyrosine kinase inhibitor (TKI) therapy including imatinib, dasatinib or nilotinib.

This application is supported by a supplemental analysis CML-300 in a subset of patients from studies CML-202 and CML-203, who received ≥ 2 approved TKIs and had evidence of resistant or intolerant to dasatinib and/or nilotinib. Studies CML-202 and CML-203 were pivotal trials in a previous New Drug Application (NDA 22-374) for omacetaxine seeking an indication as the treatment of patients with CML who have failed imatinib and have the T3151 mutation. NDA 22-374 was withdrawn by the applicant after an advisory committee voted to require a well characterized in vitro diagnostic test for T3151 mutation status confirmation. A subsequent agreement between the applicant and the Agency was reached that a combined dataset of a homogeneous patient population with respect to prior approved TKI studies CML-202 and CML-203 could be the basis of an NDA in a third-line setting. The homogeneous patient population could be patients with CML who have failed imatinib (as in study CML-202) or who failed or have intolerance to 2 or more TKI therapies (as in study CML-203).

Analysis CML-300 included 122 CML patients in either chronic phase (n = 81) or accelerated phase (n = 41) of their disease. FDA's efficacy population excluded 3 chronic phase patients enrolled in study site 22 or 30 for findings of deviations from regulations as determined by the Division of Scientific Investigations. Patients received initial induction therapy consisting of SC omacetaxine 1.25 mg/m^2 BID for 14 consecutive days every 28 days, up to 6 cycles. Responding patients were administrated with omacetaxine 1.25 mg/m^2 BID for 7 consecutive days every 28 days as the maintenance treatment, for up to 24 months. The primary efficacy endpoint for chronic phase CML was major cytogenetic response (MCyR), which included complete and partial cytogenetic responses. The primary efficacy endpoint for accelerated phase CML was major hematologic response (complete hematologic response or no evidence of leukemia) and/or MCyR. Based on data from 119 patients in the FDA efficacy analysis population, the major cytogenetic response rate in chronic phase patients was 20% with median response duration of 17.7 months, and the major hematologic response rate was 27% in accelerated phase patients with median response duration of 9.0 months. The primary endpoint result by number of prior approved TKIs received, as shown in Table 10, suggested a higher clinical response for omacetaxine as a third-line therapy.

Statistical issues with this application include: 1) The application is not supported by randomized studies; 2) Analysis CML-300 sample size is not driven by any statistical considerations; 3) A correlation between treatment response and overall survival has never been established in CML patients who have failed prior approved TKIs; 4) The estimation of response and duration of response may be influenced by the presence of best response at study entry and the duration of follow-up for treatment response.

Efficacy data for this application came from single-arm studies without any pre-specified statistical considerations. Therefore, there is no formal statistical conclusions can be made. The efficacy results and discussions presented in this review will need to be considered along with safety results and available treatment options from clinical perspectives.

2 INTRODUCTION

2.1 Overview

Proposed Indication

The applicant is seeking for omacetaxine mepesuccinate to be indicated for the treatment of adult patients with chronic or accelerated phase chronic myelogenous leukemia (CML) with resistance and/or intolerance to prior tyrosine kinase inhibitor (TKI) therapy including imatinib, dasatinib or nilotinib.

Background

CML is a clonal disease of the hematopoietic stem cell. In the United States, CML is diagnosed in approximately 5000 patients every year and accounts for about 7-15% of adult leukemias. CML has a triphase clinical course: an initial indolent chronic phase (CP), an accelerated phase (AP), and a terminal blast phase (BP). The median survival from diagnosis for CML patients is about 4-6 years, with slightly over a year and months of survival after development of accelerated phase and after blast transformation, respectively.

The treatment paradigm for CML changed in 2001 when imatinib, the first TKI, was approved. Subsequently, new TKIs including dasatinib and nilotinib were developed and approved for CML patients who became resistant to or intolerant of imatinib. Both dasatinib and nilotinib first received an accelerated approval based on cytogenetic responses in CP patients and hematologic responses in AP patients from single-arm phase 2 studies. The approval was converted to regular approval when results of those phase 2 studies with 24-month follow-up were submitted. At the time of this NDA submission, there are currently no approved treatment options for patients who have failed 2 TKIs.

Omacetaxine mepesuccinate is a first-in-class cephalotaxine. It is a inhibitor of protein synthesis, and has been developed for the treatment of CML for its potential activity in CML independent of the mutation status of Bcr-Abl.

Regulatory Communications

There was a previous NDA filling (NDA 22-374) for omacetaxine seeking an indication as the treatment of patients with CML who have failed imatinib and have the T3151 mutation. An advisory committee (Oncology Drug Advisory Committee, 03/22/2010) voted to require a well characterized in vitro diagnostic test for T3151 mutational status confirmation. Subsequently, NDA22-374 was withdrawn.

A Type A meeting was held on June 30 of 2010, and an agreement was reached that a combined dataset of a homogeneous patient population with respect to prior approved TKI from NDA 22-374 pivotal studies CML-202 and CML-203 could be the basis of an NDA in a third-line setting. The homogeneous patient population could be patients with CML who have failed imatinib (as in study CML-202) or who failed or have intolerance to 2 or more TKI therapies (as in study CML-203).

At the pre-NDA meeting held on September 28 of 2010, the applicant and the Agency discussed a supplemental analysis (Analysis CML-300) in a subset of patients from studies CML-202 and CML-203, who received 2 or more approved TKIs and had evidence of resistant or intolerant to dasatinib and/or nilotinib. This supplemental analysis forms the basis for the indication for which approval is being sought in this application.

Clinical Studies

As agreed with the applicant, review of this application will be based on data from Analysis CML-300. Table 1 provides key information on the studies CML-202, CML-203 and CML-300.

Table 1: Specific Studies Reviewed

Study no.	Population, phase, and study design	Number of patients	Treatment	Primary Efficacy endpoint
Initial Pivotal Studies				
202	Open-label, single-arm, phase II trial for efficacy and safety CML patients with T3151 Bcr-Abl gene mutation	Total: 103 (US 44 or 43%) CP / AP / BP: 62 / 20 / 21	Induction: 1.25 mg/m^2 SC BID × 14 days q28 days, up to 6 cycles Maintenance (in responding patients): 1.25 mg/m^2 SC BID × 7 days q28 days, up to 24 months	Proportion of patients achieving an overall hematologic response (OHR) or a major cytogenetic response (MCyR) , within a disease phase
203	Open-label, single-arm, phase II trial for efficacy and safety CML patients who have failed or are intolerant to TKI	Total: 100 (US 40 or 40%) CP / AP / BP: 46 / 31 / 23	The same as study 202	The same as study 202
Supplemental Analysis				
300	Subset analysis of patients who had received at least 2 approved TKIs and had prior TKI refractory/intolerance from studies 202 and 203	Total: 122 (US 50 or 41%) CP / AP / BP : 81 / 41 / 0	The same as above	DMC adjudicated treatment response CP: MCyR AP: Major hematologic response (MaHR) and/or MCyR

CP=Chronic Phase; AP=Accelerate Phase; BP=Blast Phase; SC=subcutaneous; BID=twice a day; US=United States

2.2 Data Sources

Material reviewed for this application: applicant study reports, submitted datasets for Analysis CML-300, and referenced literature on previously approved TKIs for CML.

Reviewed data were provided electronically with SDTM data formats. SAS programs for key efficacy tables were submitted in this application. The electronic path of Analysis CML-300 datasets is: cdsesub1\evsprod\NDA203585\0000\m5\datasets\c41443-suppl-analysis-cml-300.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data from initial pivotal studies CML-202 and CML-203 and from the supplemental analysis CML-300 were provided electronically with standard formats. Documentations on statistical methods and programming were included with sufficient details for this reviewer to reproduce the applicant's key efficacy results. However, data from study sites 22 and 30 were determined to be un-reliable by the Division of Scientific Investigations (DSI) because of critical findings for deviations from regulations. *Data from sites 22 and 30 will not be used in this review.*

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

This application is supported by data from Analysis CML-300: an analysis of subsets of patients enrolled in the initial NDA 22-374 pivotal studies CML-202 and CML-203 (see section 2 for previous regulator communications and designs of studies CML-202 and CML-203). Eligible patients for Analysis CML-300 were those with: CML-CP or CML-AP; who received 2 or more approved TKIs (e.g., imatinib, dasatinib, and nilotinib); and, at a minimum, had evidence of resistance or intolerance to dasatinib and/or nilotinib.

The primary efficacy endpoint for chronic phase CML was major cytogenetic response (MCyR), which included complete and partial cytogenetic responses. The primary efficacy endpoint for accelerated phase CML was major hematologic response (MaHR), which included complete hematologic response (CHR) and no evidence of leukemia (NEL).

Efficacy analyses were performed separately by disease phase, because of different disease characteristics between different disease phases. There were two pre-specified subgroup analyses: one is based on number of prior approved TKIs received, and the other is based on resistance and/or intolerance to those approved TKIs.

3.2.2 Statistical Methodologies

Sample size calculation is not applicable to supplemental analysis CML-300, because the study size was not driven by any statistical considerations.

For response rates, summary statistics include numbers and percentages of patients with response and the exact one-sided lower 95% confidence limit were reported. For time-to-event variables, statistics reported include number and percentage of censored, median and the 95% confidence interval for the median using the Kaplan-Meier product-limit estimate.

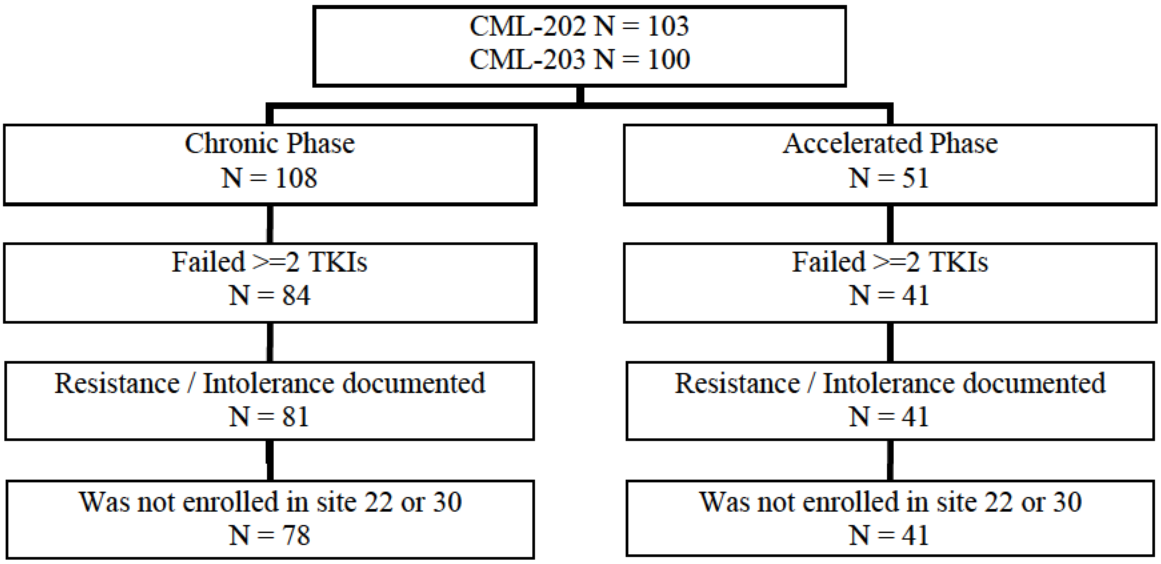
This reviewer made modifications and additional analyses to the applicant's analyses, as follows:

- Excluded 3 patients enrolled in sites 22 and 30, because there were critical findings of deviations from regulations so the data from those sites was determined to be un-reliable by the Division of Scientific Investigations. The remaining 119 Analysis CML-300 patients will be referred to as FDA efficacy analysis population hereafter.
- Reported 2-sided confidence intervals for the response rates, in order to be consistent with how the Agency reports response rate results.
- Obtained response rates after removing patients who were characterized as responders at study entry. This additional analysis was performed in consideration that a response at baseline may not represent a treatment-induced response.
- Performed a 24-week landmark analysis, which has been used in the evaluation of other therapies.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Figure 1 shows the patient criteria for FDA efficacy analysis population. The FDA efficacy analysis population included a total of 119 patients, 78 patients in the chronic phase and 41 patients in the accelerated disease phase.

Figure 1: Patient Criteria for Inclusion in FDA Efficacy Analysis Population



A summary of patient disposition for the FDA efficacy analysis population is presented in Table 2. Thirteen CP patients and two AP patients were still ongoing in their respective studies at the time of data cutoff (07 January 2011). The main reasons for withdrawal from study treatment were disease progression and lack of efficacy. The median study follow-up time, estimated by Kaplan-Meier method in all patients, was 18.6 months and 11.5 months for CP and AP patients respectively. The median study follow-up time in ongoing follow-up patients (patients who were being followed-up for survival and had not died up to the data cutoff date) was 20.0 months with a range of 2.6 to 47.7 months in the CP patients, and was 15.7 months with a range of 1.3 to 43.5 months in the AP patients.

Table 2: Disposition of Patients (FDA Efficacy Analysis Population)

	Chronic Phase N = 78	**Accelerated Phase N = 41**
Study Status, n (%)		
Ongoing	13 (16.7)	2 (4.9)
Discontinued	65 (83.3)	39 (95.1)
Duration of Study Participation (months)		
Patient ongoing (censored), n (%)	13 (16.7)	2 (4.9)
Median (95% confidence interval)	9.0 (7.1 – 11.8)	3.4 (1.9 – 6.4)
Primary Reason for Discontinuation of Study Treatment, n (%)		
Lack of efficacy	10 (12.8)	7 (17.1)
Lost to follow-up	1 (1.3)	0
Non-compliance with study drug	2 (2.6)	0
Withdrawal by patient	11 (14.1)	5 (12.2)
Progressive disease	24 (30.8)	20 (48.8)
Adverse event	6 (7.7)	2 (4.9)
Death	4 (5.1)	5 (12.2)
Other	7 (9.0)	0
Study Follow-up Time (months) – All Patients		
Patient with survival follow-up or died, n (%)	64 (82.1)	38 (92.7)
Patients with survival follow-up (censored), n (%)	14 (17.9)	3 (7.3)
Median (95% confidence interval)	18.6 (14.4 – 23.1)	11.5 (6.8 – 16.0)
Study Follow-up Time (months) – Ongoing Patients		
Patient with ongoing survival follow-up, n (%)	35 (44.9)	13 (31.7)
Median (Minimum, Maximum)	20.0 (2.6, 47.7)	15.7 (1.3, 43.5)

Reviewer Comment: As previously agreed, 24-month follow-up data on all patients could support conversion to full approval. This criterion has *not* been satisfied at this time.

Table 3 summarizes the baseline characteristics of the 119 patients included in the review for efficacy. The majority of patients were white and male. The median age was 60 years with a range of 23 to 83 years. About a quarter of these patients had a complete hematologic response status at baseline, and 50% of these patients had failed all 3 approved TKIs. The most frequently used non-TKI leukemia treatments were hydroxyurea, interferon, and cytarabine.

Table 3: Demographics and Baseline Characteristics (FDA Efficacy Analysis Population)

	Chronic (n=78)	**Accelerated (n=41)**	**Total (n=119)**
Age (years)			
Median (Minimum, Maximum)	59 (29, 83)	63 (23, 83)	60 (23, 83)
% >=65 years of age	29	46	35
Sex			
% Male	62	61	61
Race			
% White / Black / Asian / Hispanic	81 / 5 / 4 / 4	68 / 24 / 2 / 2	76 / 12 / 3 / 3
ECOG performance status, %			
0 / 1 / 2	67 / 31 / 3	29 / 54 / 17	54 / 39 / 8
Time from CML diagnosis (months)*			
Median (Minimum, Maximum)	73 (8, 234)	98 (23, 286)	83 (8, 286)
Baseline CHR status			
% CHR+	29	22	27
Failed previous leukemia treatment, %			
Imatinib & Dasatinib	38	34	37
Imatinib & Nilotinib	15	7	13
Imatinib & Dasatinib & Nilotinib	46	59	50
Previous non-TKI treatment used by >10% of patients, %			
Hydroxyurea	54	46	51
Interferon	33	32	33
Cytarabine	31	29	30

* Calculated by the reviewer as (date of first dose – date of first diagnosis of CML + 1) / (365/12)

3.2.4 Results and Conclusions

3.2.4.1 Response Rates

Table 4 shows the applicant's results on response rates using data from 122 analysis CML-300 patients. Table 5 shows the results on response rates using data from 119 patients in the FDA efficacy analysis population. The numbers in bold represent the primary endpoints for approval. Based on FDA's efficacy analysis population, the clinical response rate was 20.5% with a 2-sided lower 95% confidence limit of 12.2% in the chronic phase patients, and was 26.8% with a lower limit of 14.2% in the accelerated phase patients. Among the CP patients who had a major

cytogenetic response, half of them achieved a complete response. All but one of the major hematologic responses were complete responses.

These reported responders included patients who presented with a best response at study entry.

Table 4: Clinical Response Rate by Disease Phase (Analysis CML-300 Patients)

	Chronic phase (n = 81)		Accelerated phase (n = 41)	
	n	**% (95% CI)**	**n**	**% (95% CI)**
Hematologic response rate				
MaHR	NA	NA	11	**26.8[*] (14.2 – 42.9)**
CHR	56	69.1 (57.9 – 78.9)	10	24.4 (12.4 – 40.3)
NEL	NA	NA	1	2.4 (0.0 – 12.9)
Cytogenetic response rate				
MCyR	16	**19.8[*] (11.7 – 30.1)**	0	-
CCyR	8	9.9 (4.4 – 18.5)	0	-

[*] Including patients presented with best response at study entry

[*] CI = confidence interval; MaHR = major hematologic response; CHR = complete hematologic response; NEL = no evidence of leukemia; MCyR = major cytogenetic response; CCyR = complete cytogenetic response

Table 5: Clinical Response Rate by Disease Phase (FDA Efficacy Analysis Population)

	Chronic phase (n = 78)		Accelerated phase (n = 41)	
	n	**% (95% CI)**	**n**	**% (95% CI)**
Hematologic response rate				
MaHR	NA	-	11	**26.8[*] (14.2 – 42.9)**
CHR	55	70.5 (59.1 – 80.3)	10	24.4 (12.4 – 40.3)
NEL	NA	-	1	2.4 (0.0 – 12.9)
Cytogenetic response rate				
MCyR	16	**20.5[*] (12.2 – 31.2)**	0	-
CCyR	8	10.3 (4.5 – 19.2)	0	-

[*] Including patients presented with best response at study entry

[*] CI = confidence interval; MaHR = major hematologic response; CHR = complete hematologic response; NEL = no evidence of leukemia; MCyR = major cytogenetic response; CCyR = complete cytogenetic response

3.2.4.2 Onset and Duration of Response

Table 6 summarizes the time to onset and duration of response in responders. The median time to response among responders was reported to be 2.6 months and 0 month for the chronic phase and accelerated phase patients respectively. The estimated median duration of response was 17.7 months for the chronic phase patients, and 9.0 months for the accelerated phase patients.

The time to onset and duration of response calculations included 2 chronic phase patients and 6 accelerated phase patients who had a best response at study entry.

Table 6: Onset and Duration of Response in Responders

	Chronic phase (MCyR)	Accelerated phase (MaHR)
Number of responders	16	11
Time to Onset of Response (months)[1]		
Mean, Median	3.1, 2.6	1.1, 0.0
Minimum, Maximum	0.0[*], 6.3	0.0[#], 4.2
Duration of Response (Months)[1]		
Median	17.7	9.0
95% CI	4.1 - NA	3.6 – 14.1

[1] Values are for those patients who did respond
[*] Two responders had "best cytogenetic response at study entry"
[#] Six responders had "best hematologic response at study entry"
MCyR = major cytogenetic response; MaHR = major hematologic response

3.2.4.3 Progression-Free Survival and Overall Survival

Table 7 and Table 8 summarize results of progression-free survival and overall survival. The median time to progression was 9.7 months for the chronic phase (CP) patients, and 4.7 months for the accelerated phase (AP) patients. The median overall survival was 33.9 months for the CP patients, and was 16.2 months for the AP patients.

Table 7: Summary of Progression-Free Survival (FDA Efficacy Analysis Population)

	Chronic Phase (N = 78)	Accelerated Phase (N = 41)
Number (%) of patients who progressed	57 (73.1%)	38 (92.7%)
Number (%) of patients censored	21 (26.9%)	3 (7.3%)
Median (months)	9.7	4.7
95% CI of median	7.0 – 12.0	2.1 – 7.0

Table 8: Summary of Overall Survival (FDA Efficacy Analysis Population)

	Chronic Phase (N = 78)	Accelerated Phase (N = 41)
Number (%) of patients who died	29 (37.2%)	25 (61.0%)
Number (%) of patients didn't die (censored)	49 (62.8%)	16 (39.0%)
Median (months)	33.9	16.2
95% CI of median	20.3 - NA	8.2 – 24.6

Reviewer Comment: Time to event analyses are not interpretable in single-arm studies.

3.2.4.4 Subgroup Analyses

Table 9 displays the primary endpoint result by demographics. CP patients who were younger than 65 years of age had a higher response rate compared to the older patients. But for the AP patients, a much lower hematologic response rate was observed in patients younger than 65 compared to the ones who were at least 65 years of age. For both disease phase groups, men had a higher response rate compared to women. With respect to race, comparable results were found between Caucasians and non-Caucasians.

Table 9: Clinical Response Result by Demographics (FDA Efficacy Analysis Population)

	Chronic phase (MCyR)		Accelerated phase (MaHR)	
	n / N	**%**	**n / N**	**%**
Age (years)				
< 65	14 / 55	25.5	3 / 22	13.6
>= 65	2 / 23	8.7	8 / 19	42.1
Sex				
Male	11 / 48	22.9	8 / 25	32.0
Female	5 / 30	16.7	3 / 16	18.8
Race				
Caucasian	13 / 63	20.6	8 / 28	28.6
Non-Caucasian	3 / 15	20.0	3 / 13	23.1

MCyR = major cytogenetic response; MaHR = major hematologic response

The primary endpoint result by number of prior approved TKIs received, as shown in Table 10, suggested a higher clinical response for omacetaxine as a third-line therapy. Only a few patients did not belong to the resistant to ≥ 2 TKIs category, the response result by resistance/intolerance status was not informative.

Table 10: Clinical Response Result by Number of and Resistance/Intolerance Status to Approved TKIs Received (FDA Efficacy Analysis Population)

	Chronic phase (MCyR)		Accelerated phase (MaHR)	
	n / N	**%**	**n / N**	**%**
Number of Approved TKIs Received				
2 TKIs	12 / 42	28.6	6 / 17	35.3
3 TKIs	4 / 36	11.1	5 / 24	20.8
Resistance/Intolerance Category				
Resistant to ≥ 2 TKIs	13 / 67	19.4	10 / 36	27.8
Intolerance to ≥ 2 TKIs	2 / 7	28.6	0 / 3	0.0
Intolerant to 1 TKI and resistant to another	1 / 4	25.0	1 / 2	50.0

MCyR = major cytogenetic response; MaHR = major hematologic response; TKI = tyrosine kinase inhibitor

3.2.4.5 Additional Analyses

One additional analysis is to re-calculate the clinical response after excluding patients who were characterized by DMC as responders at study entry. Table 11 gives clinical response results, after excluding two patients in chronic phase and six patients in accelerated phase who were characterized as responders at study entry. The consideration is that the responses in these responders were not the same as the other treatment-induced responses. The re-calculations resulted in different response rates from the ones reported in Table 5, with a response rate of 18.4% (95% CI: 10.5 – 29.0%) for the chronic phase patients and a response rate of 14.3% (95% CI: 4.5 – 30.3%) for the accelerated phase patients. The median time to response in patients who responded after administration of study treatment was calculated to be around 2 to 3 months. The median duration of response was estimated to be 12.5 months for the CP responders and 4.7 months for the AP responders, compared to 17.7 months and 9.0 months as reported in Table 6 including the non treatment-induced responses.

Table 11: Clinical Response Excluding Patients Presented with Best Response at Study Entry

	Chronic phase (N = 76)	**Accelerated phase (N = 35)**
Responders*		
n, % (95% confidence interval)	14, 18.4% (10.5% - 29.0%)	5, 14.3% (4.5% - 30.3%)
Time to Onset of Response (months)[1]		
Mean, Median	3.5, 2.8	2.3, 2.5
Minimum, Maximum	1.2, 6.3	1.0, 4.2
Duration of Response (Months)[1]		
Median	12.5	4.7
95% confidence interval	3.5 – NA	3.6 – NA

[1] Values are for those patients who did respond; * Chronic phase patients who achieved a major cytogenetic response, or accelerated phase patients who achieved a major hematologic response

The other additional analysis is to perform a 24-week landmark analysis, which has been used in the evaluation of other therapies. This analysis was performed based on investigator's response assessment, because the DMC response dataset only has the best response determination and does not have all the response assessment outcomes and assessment dates to allow a landmark analysis. This landmark analysis removed 5 CP responders and 1 AP responder, if the response was followed up to 24 weeks since the start of treatment.

Table 12: Twenty-four Week Landmark Analysis of Clinical Response

	Chronic phase (MCyR)	**Accelerated phase (MaHR)**
Response up to 24 weeks of follow-up, with responders at study entry		
n / N	11 / 78	10 / 41
% (95% confidence interval)	14.1 (7.3 – 23.8)	24.4 (12.4 – 40.3)
Response up to 24 weeks of follow-up, without responders at study entry		
n / N	9 / 76	4 / 35
% (95% confidence interval)	11.8 (5.6 – 21.3)	11.4 (3.2 – 26.7)

MCyR = major cytogenetic response; MaHR = major hematologic response

3.2.4.6 Statistical Issues and Conclusion

There are a few statistical issues with the determination of treatment efficacy:

- The application is based on data from single-arm trials and therefore no statistical inference can be made
- The sample size for analysis population is not driven by any statistical considerations
- Due to the lack of randomized data, the predictability of treatment response for overall survival in CML patients has never been established
- It is difficult to interpret the treatment response rate in the content of time, because of the presence of best responses at study entry and the lack of adjudicated response data for landmark analyses

Based on data from the supplemental analysis CML-300, the applicant reported a major cytogenetic response rate of 19.8% with median response duration of 17.7 months in chronic phase patients, and a major hematologic response rate of 26.8% with median response duration of 9.0 months in accelerated phase patients. The FDA's efficacy analysis population excluded 3 CML-CP patients from study sites 22 and 30 for regulatory deviations as determined by the Division of Scientific Investigations. This exclusion changed the major cytogenetic response rate only slightly to 20.5% in the CP patients.

However, the reviewer's additional analyses found the estimation of response and duration of response may be influenced by the presence of best response at study entry and the duration of follow-up for treatment response.

3.3 Evaluation of Safety

There are no specified statistical considerations for safety analyses in this application. Please refer to Dr. Alvandi's review for detailed safety evaluation and clinical interpretation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses of response rate by age (<65, >=65 years), gender (male, female), and race (Caucasian, non-Caucasian) are available in Table 9.

The 119 FDA efficacy analysis population patients were studied in 10 different countries (Canada, Germany, France, United Kingdom, Hungary, India, Italy, Poland, Singapore, and United States). Twenty-eight (or 35.9%) of the 78 CML-CP patients and 22 (or 53.7%) of the 41 CML-AP patients were enrolled in the United States. Subgroup analysis revealed comparable MCyR rates between USA and non-USA CML-CP patients (21.4% versus 20.0%), and a higher MaHR rate in USA CML-AP patients compared to non-USA CML-AP patients (40.9% versus 10.5%).

4.2 Other Special/Subgroup Populations

Subgroup analyses of response rate by number of prior approved TKIs, and resistance and/or intolerant to prior approved TKIs can be found in Table 10.

Reviewer Comment: Although there were different efficacy results in sub-populations, there were no specified testing between subgroups and the sizes of the sub-populations were too small to draw any statistical conclusions for comparisons between subgroups of patients.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are a few statistical issues for this application. First, the application is based on single-arm trials and therefore no statistical inference can be made. Second, the sample size for the analysis population is not driven by any statistical considerations. Third, due to the lack of randomized data, the predictability of treatment response for overall survival of CML patients has never been established. Fourth, it is difficult to interpret the treatment response rate in the content of time, because of the presence of best responses at study entry and the lack of adjudicated response data for landmark analyses.

5.2 Collective Evidence

In summary, based on data from 119 patients in the FDA efficacy analysis population, the major cytogenetic response rate in chronic phase patients was 20% with median response duration of 17.7 months, and the major hematologic response rate was 27% in accelerated phase patients with median response duration of 9.0 months. However, the estimation of response and duration of response may be influenced by the presence of best response at study entry and the duration of follow-up for treatment response. In particular, the response rate changed to 18.4% in the chronic phase patients, and 14.3% in the accelerated phase patients, when the patients who were characterized as responders at study entry were removed from the response calculations.

5.3 Conclusions and Recommendations

Efficacy data for this application came from single-arm studies without any pre-specified statistical considerations. Therefore, no formal statistical conclusions can be made. The efficacy results and discussions presented in this review will need to be considered along with safety results and available treatment options from clinical perspectives.

5.4 Labeling Recommendations

This reviewer recommends 3 changes to the applicant's proposed labeling be considered:

1. Remove data from sites 22 and 30 per recommendation from DSI;
2. Replace the applicant's results on response rate and duration of response with the FDA results, which did not include patients who were characterized by DMC as responders at study entry;
3. Remove the (b) (4) results from single-arm studies.

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/s/

CHIA-WEN KO
09/05/2012

MARK D ROTHMANN
09/05/2012
I concur

RAJESHWARI SRIDHARA
09/05/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: NDA203585 **Applicant:** Cephalon, Inc. **Stamp Date:** 03/30/2012

Drug Name: omacetaxine **NDA/BLA Type:** Original NDA Application

On **initial** overview of the NDA/BLA application for RTF: There are no filling issues - all necessary documents are available to allow statistical review to begin.

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			There were 2 pre-specified subgroup efficacy analyses: (1) number of prior approved TKI (2 vs. 3 approved TKI); (2) resistance and/or intolerant to prior TKI (resistant, intolerant, resistant to one and intolerant to the other)
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			From the 30June2010 Type A Meeting Minutes: "The Agency agreed that a combined data set of a homogeneous patient population with respect to prior therapy from studies 202 and 203 could be the basis of an NDA in a third-line setting." According to the 13Sep2010 meeting minutes, the FDA answered Yes to these 2 questions: (1) "Based on 21

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

				CRF 314 Subpart H, would the enclosed supplemental analysis of studies CML-202 and CML-203 satisfy the requirements for a registration based on endpoints that are reasonably likely to predict clinical benefit?"; (2) "Would the design of Studies CML-202 and CML-203 ultimately support clinical benefit to confer a regular approval?"
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	Interim conditional power monitoring for sample size re-adjustment was in the original protocols (CML-202 and CML-203), but was discontinued following discussions with the Agency. There were no interim analyses.
Appropriate references for novel statistical methodology (if present) are included.			X	Analyses did not involve novel statistical methodology
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			• Single arm studies • Only observed data were considered in the clinical response assessments. Missing values (other than partial missing dates) were not imputed. Data listings were created to summarize the number of discontinued patients, the reasons for discontinuation, and the treatment exposure and duration in the discontinued patients.

Chia-Wen Ko 05/11/2012

Reviewing Statistician Date

Mark Rothmann 05/11/2012

Supervisor/Team Leader Date

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/s/

CHIA-WEN KO
05/11/2012

MARK D ROTHMANN
05/11/2012