CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203585Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

NDA: **203585**	Submission Date: **March 30, 2012**
Generic Name	**Omacetaxine mepesuccinate**
Reviewer	**Jee Eun Lee, Ph.D.**
Secondary Reviewer	**Kevin Krudys, Ph.D.**
OCPB Division	**DCP-5**
ORM division	**OND/ OHOP/DHP**
Sponsor	**Cephalon Inc.**
Formulation; Strength(s)	**3.5 mg Lyophilized Powder in a Single-Use Vial**
Indication	**Treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI)**

1 SUMMARY OF FINDINGS

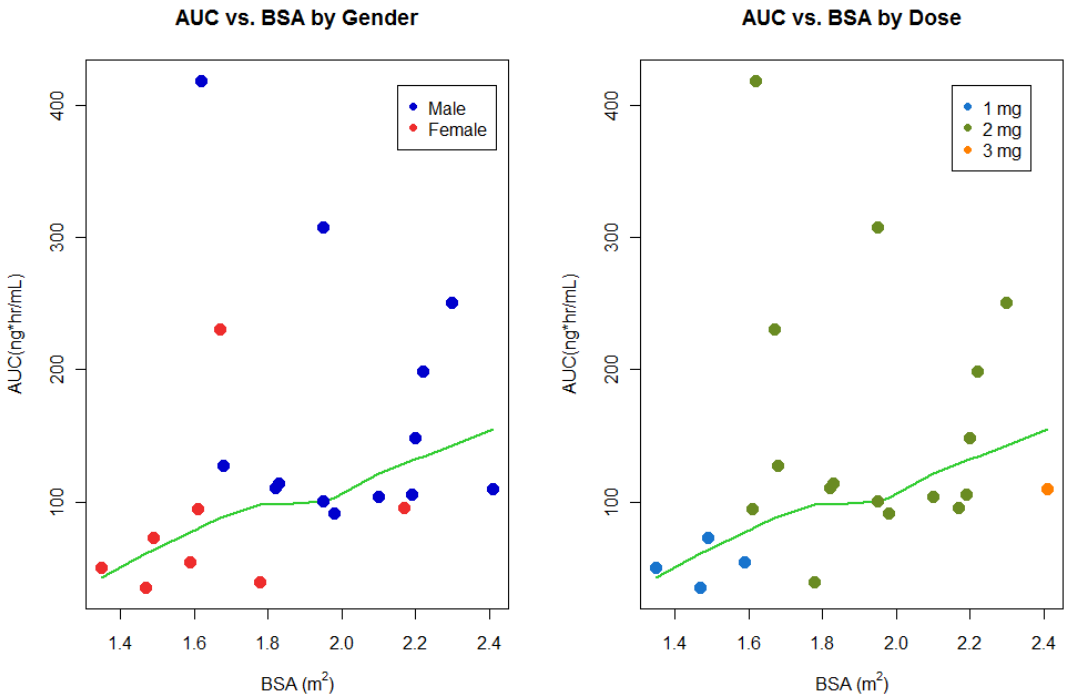
1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is body surface area-based dosing appropriate for omacetaxine?

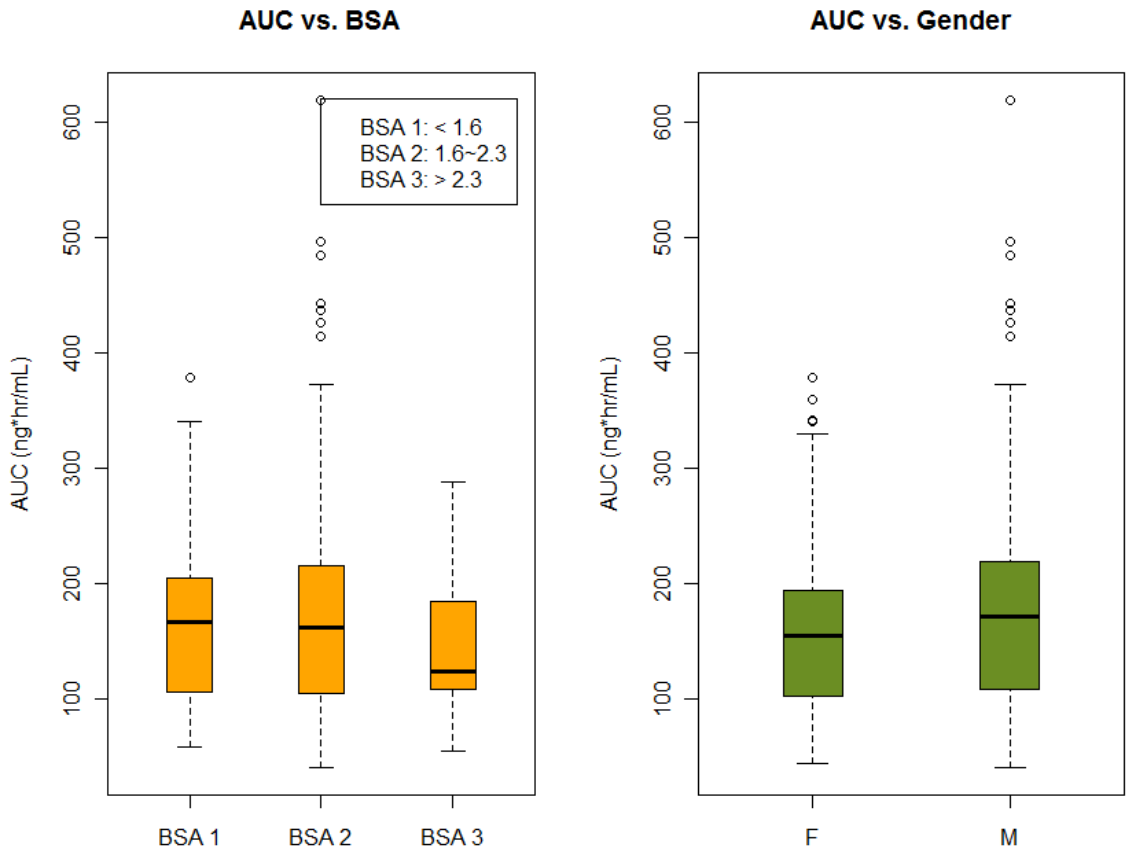
No. The reviewer's analysis found that clearance of omacetaxine was not correlated with BSA and thus BSA-based dosing might fail to achieve effective concentrations in patients with lower body size, such as women. An effect of gender on efficacy was observed from a subgroup analysis of the pivotal trials. For CML-CP patients, the primary endpoint, MCyR rates was 22% in men and 16% in women. The secondary endpoint, MaHR rate was 71% in men and 66% in women. For CML-AP patients, the primary endpoint, MaHR rate was 32% in mean and 19% in women. The effect of gender on exposure is noteworthy but it is rather attributable to lower dosing in female patients who have lower body surface area (BSA) when clearance was not correlated with BSA (Figure 1).

Figure 1. Exposures of omacetaxine vs. BSA by Gender and Dose Following BSA-Based Dosing



Simulation with estimated parameters from the population PK model was performed to predict exposure following a fixed dosing regimen. The median dose of 2 mg was chosen for the simulation. As shown in Figure 2, the predicted exposure following a fixed dose becomes comparable across BSA and thus the effect of gender disappears.

Figure 2. Boxplots for Simulated AUC of Omacetaxine by BSA and Gender Following Fixed Dose of 2 mg



1.1.2 Are the proposed labeling statements supported by the sponsor's modeling and simulation?

No. The sponsor's analysis was insufficient to address the effects of demographic covariates on omacetaxine pharmacokinetics. As a result of an insufficient range of renal function in patients, the effect of renal/hepatic function on omacetaxine exposure could not be adequately evaluated. Only a small number of patients with moderate renal impairment (N=2) and severe renal impairment (N=1) were included. No patients with moderate or severe hepatic impairment were included. Thus the negative results for the effect of renal/hepatic impairment on omacetaxine exposure are not acceptable.

1.2 Recommendations

The submission is acceptable from a Clinical Pharmacology perspective.

1.3 Phase IV Requirements

The proposed dose of omacetaxine for treatment of chronic or accelerated phase chronic myeloid leukemia was empirically determined and the data obtained from pivotal clinical trial indicate a potential dosing inadequacy resulting in lower efficacy in patients with lower body surface area. Therefore, a study to evaluate a fixed dosing regimen that provides exposures comparable across patients is recommended as a post-marketing requirement.

1.4 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)

[redacted]

2 PERTINENT REGULATORY BACKGROUND

Omacetaxine (omacetaxine mepesuccinate) is a new molecular entity and was previously submitted for the treatment of adults with chronic myeloid leukemia (CML) who failed prior therapy with imatinib and have the Bcr-Abl T315I mutation under NDA22374. NDA22374 received a complete response in 2010 with clinical and clinical

pharmacology deficiencies. The CR letter included a recommendation for optimizing the dosing regimen in future trials since the proposed dose of 1.25 mg/m^2 had been chosen based on literature prior to two pivotal trials (CML-202 and CML-203).

The current submission includes a retrospective efficacy/safety analysis (Analysis CML-300) for subgroups (CML-AP and CML-CP who failed prior treatment of at least two TKIs) of two pivotal trials. From Analysis CML-300, the sponsor observed an effect of gender on efficacy in both CML-AP and CML-CP patients. Since none of the studies in CML patients collected PK sampling, an exposure-response relationship has not been established. The PK data in patients with hematologic malignancies (CGX-635-205) was instead utilized to address omacetaxine pharmacokinetics and the effects of demographic covariates on the exposure of omacetaxine. This study was a Phase 1, single- and multiple-dose PK study of omacetaxine in 21 patients (female=8, male=13, all Caucasian) with hematologic tumors. Intensive PK sampling occurred on Days 1 and 11 (N=21 on Day 1, N=10 on Day 11) for characterization of single-dose and steady-state PK of omacetaxine. The clinical study report including results of an NCA was originally submitted under NDA22374 by ChemGenex Pharmaceuticals. Given the exposure measures previously obtained from the NCA, the sponsor (Cephalon for current resubmission) addressed the effects of demographic covariates including gender, body-surface area, age, and renal/hepatic impairment on omacetaxine exposure in the report (CP-11-008) submitted under the current resubmission. A population approach was not utilized in the analysis.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Study CP-11-108: Covariate Analyses of Omacetaxine Measures from CGX-635-205

A substantial portion of the sponsor's analysis consisted of graphical assessments of covariates such as gender, age, body-surface area, and renal/hepatic function on the estimated exposure measures (Cmax and AUC) from the NCA. The estimated PK parameters from CGX-635-205 are summarized in Table 1.

Table 1. PK Parameters of Omacetaxine from CGX-635-205

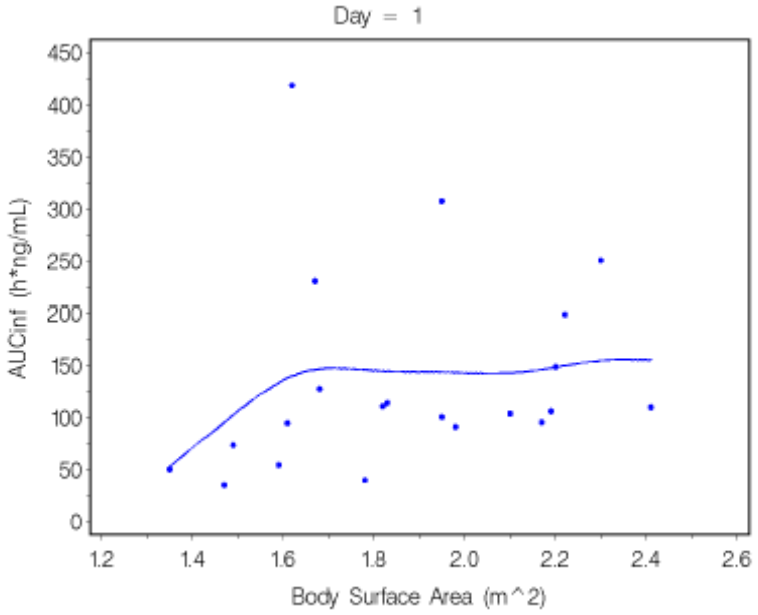
Day 1 (N=21,%CV)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	AUC∞ (ng*hr/mL)	CL/F (L/hr/m^2)[a]	V/F (L/m^2)[a]
	25.1 (56)	(0.55, 27.1)	6.96 (35)	136.2 (70.3)	13.5 (64.0)	126.8 (63.9)
Day 11 (N=10, %CV)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	AUCτ (ng*hr/mL)	CLss/F (L/hr/m^2)	Vss/F (L/m^2)
	36.2 (55.6)	0.60 (36.1)	7.03 (31.8)	188.0 (72.3)	10.5 (76.3)	66.2 (59.2)

Sponsor's report (CGX-635-205, Table 5-1 on page 15

The sponsor did not conduct further analysis on primary PK parameters (CL/F and V/F) and concluded that the effect of gender on exposure was statistically significant and partially attributed to BSA.

Representative plots for exposure versus demographic covariates (AUC∞ on Day 1 vs. BSA and gender) are provided in Figures 3 and 4.

Figure 3. Scatterplot of Day 1 AUC_{inf} versus Body Surface Area



Sponsor's report (CP-11-008) Figure 8-24 on page 44

Figure 4. Boxplot of Day 1 AUC_{inf} versus Gender

Sponsor's report (CP-11-008) Figure 8-19on page 38

Reviewer's Comments:

The sponsor's analysis was based on the data obtained from a noncompartmental analysis. One measurement from one individual for each exposure measure (Cmax on Day 1, Cmax on Day 2, AUC∞ on Day 1, and AUCτ on Day 11) was utilized in each modeling exercise. The sponsor's analysis was to compare the population prediction of exposure measures in women with the population prediction of exposure measures in men. No individual level prediction was involved. . The graphical/statistical assessments for demographic covariates were not sufficient since analysis were not conducted with primary pharmacokinetics parameters such as clearance.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The Sponsor noted that response rates tended to be higher in men compared to women. Furthermore, omacetaxine exposure was higher in men than women. An independent analysis was therefore conducted to explore the possibility that the difference in exposure by gender was due to BSA-based dosing.

4.2 Objectives

Analysis objectives are:

1. To evaluate the effect of gender or BSA on the pharmacokinetics of omacetaxine with a population pharmacokinetics model
2. To evaluate the potential relationship between the BSA-based dosing regimen and the effect of gender on efficacy observed from the sponsor's analysis (Analysis CML-300)

4.3 Methods

4.3.1 Data sets

Data sets used in the analysis are summarized in Table 2.

Table 2. Analysis Data Sets

Study Number	Name	Link to EDR
Study-cp-11-008	c205pkp3.xpt	\\cdsesub1\evsprod\NDA203585\0000\m5\datasets\cp-11-008\analysis
Study-CGX-635-205	d_adwo.xpt	\\cdsesub1\evsprod\NDA203585\0014\m5\datasets\c41443-cgx-635-205\analysis
Analysis CML-300	adsl.xpt,	\\cdsesub1\evsprod\NDA203585\0000\m5\datasets\c41443-suppl-analysis-cml-300\analysis

4.3.2 Software

Population pharmacokinetics modeling was performed with NONMEM (version 7.2) and graphical, statistical analysis and simulation were performed with R (version 2.13.1).

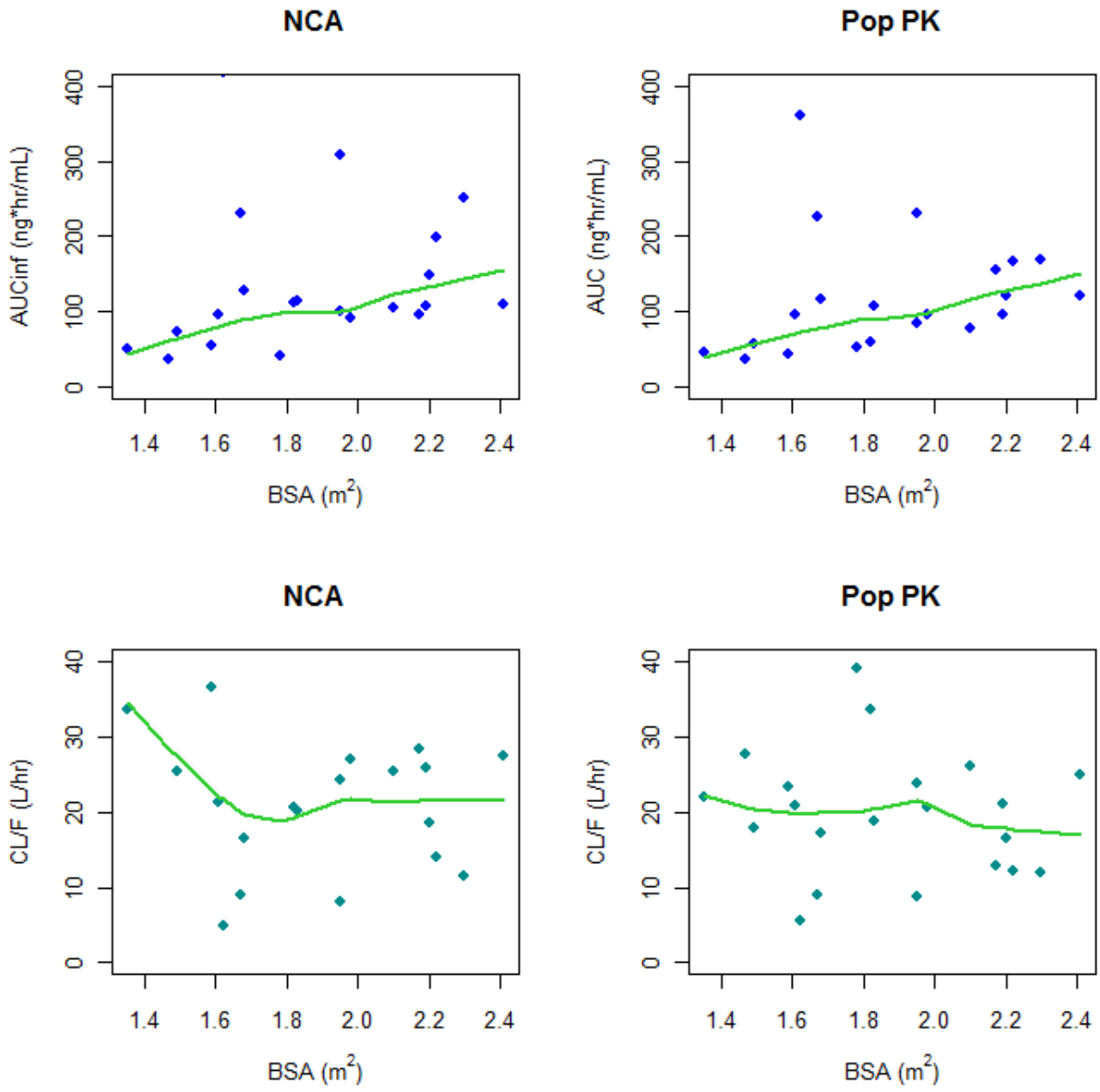
4.3.3 Population PK model

The sponsor's analysis in Study CP-11-108 was not based on individual concentration data, but on the estimated exposure measures from a non-compartmental analysis (NCA) for study CGX-635-205. The sponsor estimated clearance as BSA-normalized clearance thus a population PK model was developed to evaluate covariates such as BSA and gender. Population PK parameters were then utilized to simulate PK profiles of omacetaxine with different dosing scenario e.g., fixed-dosing regimen.

The data set included plasma concentrations of omacetaxine from 21 patients (female=8, male=13, all Caucasian) with hematologic malignancies. The median age was 58 (ranging 40-76) years and the median BSA was 1.83 (ranging 1.4~2.4) m^2. The PK sampling occurred on Days 1 and 11, however, due to the lack of information regarding missed doses and significant drop-outs, Day 1 data were only utilized for the analysis. Among the twenty one patients, eleven patients discontinued from the study due to disease progression, five patients withdrew consent, and only one subject completed Cycle 3 of the treatment.

The high clearance in patients with lower BSA observed from NCA (Figure 5) could be possibly due to nonlinear PK of omacetaxine (e.g., high clearance at low dose). However, nonlinearity cannot be assessed due to the lack of information. These high clearance estimates were associated with the female patients who received the lowest dose of 1 mg. Thus effect of gender, effect of BSA, and dose-dependent pharmacokinetics are confounded. Given that limitation, a decreasing trend in clearance with increasing BSA as seen in Figure 5 is inconsistent with physiology. Nonetheless, it is unlikely that apparent clearance is correlated with BSA. During the reviewer's analysis, concentrations at the last time point (12 hours post-dose, pre-dose of the second dose on Day 1) in three patients (IDs 1001, 1009, 1010) were found to be outliers since those concentrations were apparently obtained following administration of the second dose. After removal of those three concentration data, a total of 123 measurements were included in the analysis. Introducing a population approach changed the characteristics of the correlation between clearance and BSA while the correlation between AUC and BSA remained similar (Figure 5).

Figure 5. Comparison of Clearance from NCA and Population PK Analysis



Scatter plots for the NCA data were generated by the reviewer with the data included in study CGX-635-205(CL/F was calculated from CL/F/BSA)

A one-compartment with first order absorption model was chosen as the base model. An exponential inter-individual error model and proportional plus additive residual error model were utilized. BSA or gender was added as a covariate for clearance. As shown in Table 3, the covariate model with either BSA or gender did not reduce objective function values (OFV, log likelihood ratio) significantly (minimum ΔOFV for significance ($p< 0.05$): 3.84) compared with the base model. The results not only support the lack of

correlation of clearance and BSA observed from NCA results but also indicate the lack of correlation between clearance and gender.

Table 3. Objective Function Values for Base and Covariate Models

Model	Base	Covariate of BSA	Covariate of Gender
OFV	448.179	448.179	445.457
ΔOFV	NA	0	2.68

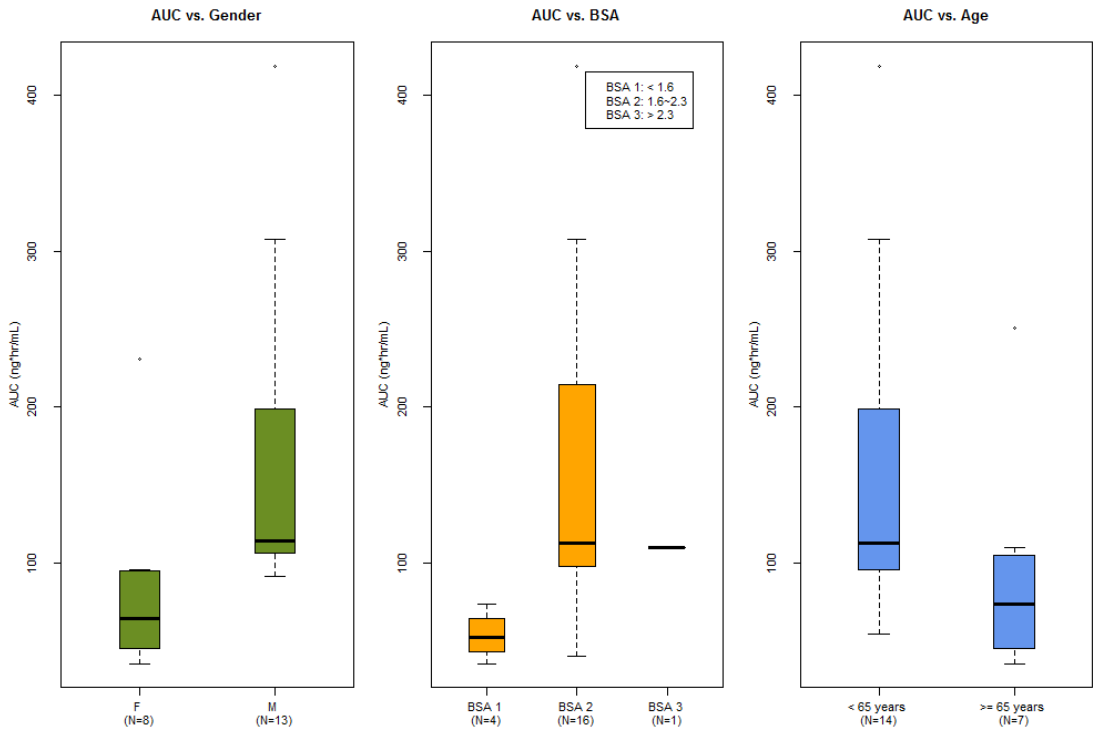
The estimated parameters from the final model for omacetaxine were summarized in Table 4.

Table 4. Estimated Parameters from Population PK Analysis

	Typical Value	CV (%)	RSE (%)
CL	13.1 (L/hr)	53	48.3
V	159 (L)	76	34.7
ka	3.74 (/hr)	503	17.5

Due to the small sample size and insufficient sampling during absorption phase, precision for the parameter estimates is small, especially for the inter-individual variability of V/F and ka (217% and 124%). As shown in Table 2, the addition of BSA in the model did not improve the fit and the estimated power for the allometric scaling factor was near zero. Even after considering the limitations of the population pharmacokinetic model, the results are consistent with the NCA and suggest that clearance is not correlated with BSA and thus challenge the need of BSA-based dosing for omacetaxine. As shown in Figure 6, the effect of gender on exposure observed from NCA results is indeed the difference in BSA; female patients have lower body surface area.

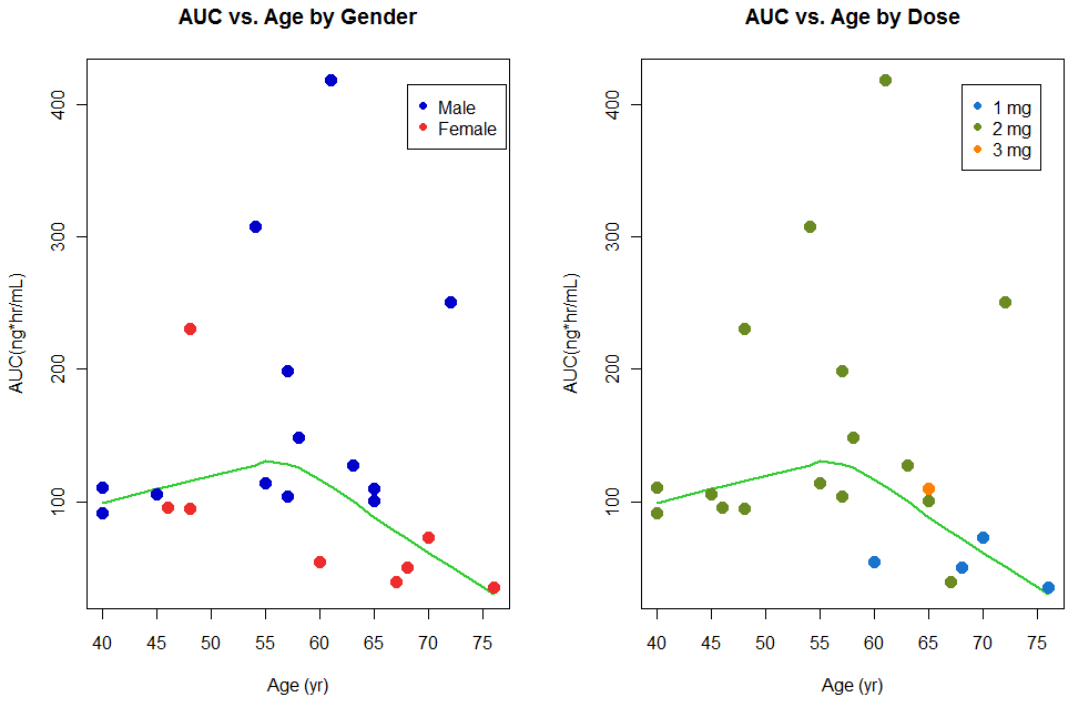
Figure 6. Boxplots for AUC of Omacetaxine by Gender, BSA and Age Following BSA-Based Dosing



The fact that those female patients received lower doses based on their lower surface area is confirmed by plots in Figure 1. The majority of patients received the median dose of 2 mg, and four female patients with lowest AUC values received 1 mg of dose while only one patient with BSA 2.4 m^2 received the dose of 3 mg. Thus, the lower exposures in women were caused by lower doses based on BSA-based dosing regimen.

The effect of age on exposure observed from NCA results (Figure 6) is also attributable to the difference in dose. As shown in Figure 7, the majority of patients > 65 years of age are women whose BSA is lower and they received lower doses. Furthermore, a relationship between age and efficacy was observed from Analysis CML-300: MCyR in CML-CP was 26% vs. 9% for patients < 65 vs. ≥ 65 years of age and MHaR CML-AP was 42% vs. 14% for patients ≥ 65 vs. < 65 years of age. The BSA in older patients tended to be lower in CML-CP and higher in CML-AP compared to younger patients. The potential correlation between lower efficacy with the lower exposure due to lower dose is also supported by the effect of age on exposure and efficacy.

Figure 7. AUC and BSA versus Age



4.3.4 Simulation with fixed dosing regimen

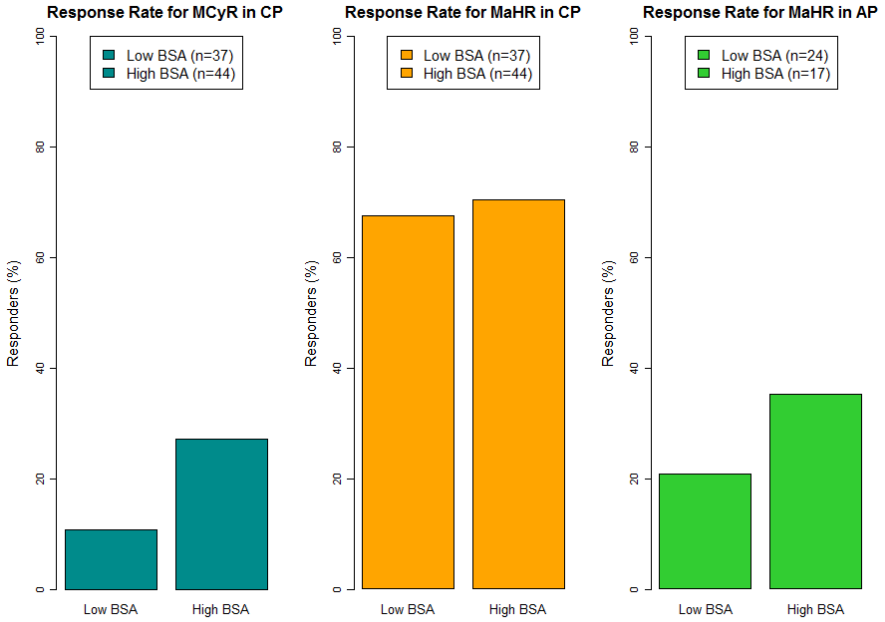
The analysis was then continued to simulate omacetaxine exposure with a fixed dosing regimen. To evaluate the exposures of omacetaxine across gender and BSA following a fixed dosing regimen, a median dose of 2 mg was chosen. The parameters estimated from the final population PK model with BSA were used for the simulation and ten replicates were produced for smoother regression.

As shown in Figure 2, administration of a fixed dose of 2 mg predicted comparable exposures across BSA and the effect of gender on exposure disappears.

4.3.5 Effect of BSA on Efficacy Results from Analysis 300

Since the exposure-response relationship has not been established for the indication of CML, the effect of BSA-based dosing on exposure was inferred by further analysis using data from Analysis 300 which includes data from two pivotal trials. As shown in Figure 8, the efficacy appears to be higher in patients with higher body surface area, although the differences in the endpoints are not statistically significant.

Figure 8. Response Rates for MCyR, MaHR by BSA

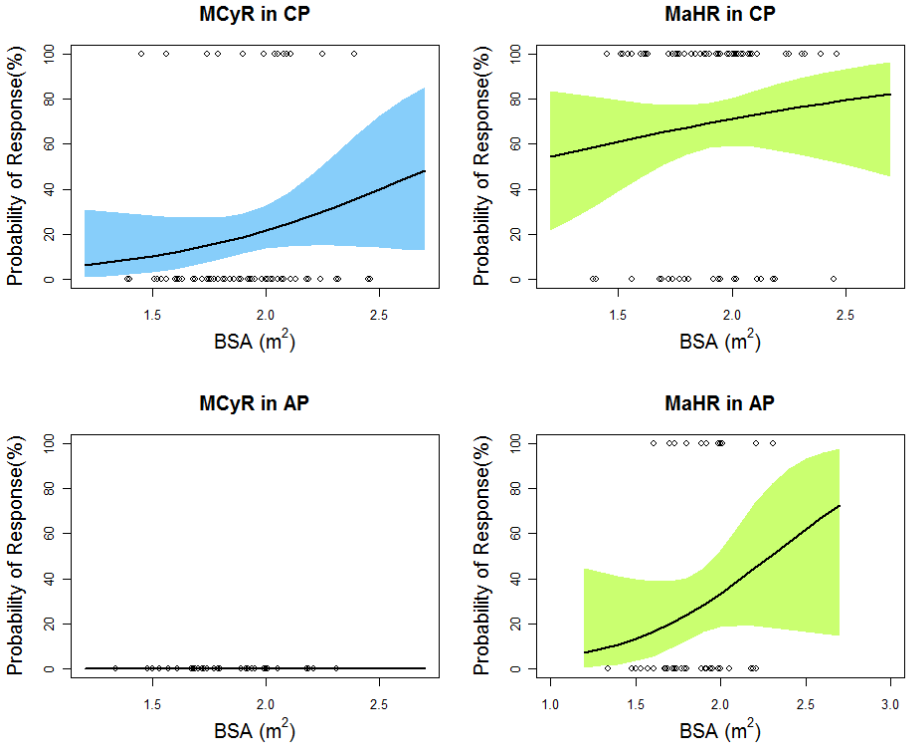


Due to the small sample size, a definitive conclusion is not feasible. Nonetheless, the increasing trend in all three endpoints is likely to support the need of increasing dose in patients with lower BSA and the potential of an optimal dose as fixed dosing regimen.

4.3.6 Logistic Regression

Logistic regression was performed as a supplementary analysis for efficacy endpoints of CML-CP and CML-AP. As shown in Figure 9, the probability of response increases as BSA increases for all three endpoints in both subgroups. Although the interpretation of this logistic regression is limited due to the small sample size, the inference of the regression supports the postulation on fixed-dosing as an alternative dosing regimen to achieve comparable exposures across gender and BSA.

Figure 9. Logistic Regression on Clinical Endpoints in CML-300



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
NDA203585_PopPK.R base.ctl bsa5.ctl gen.ctl	Population PK analysis for omacetaxine	Reviews\Ongoing PM Reviews\Omacetaxine_NDA203585_JEL\PPK Analyses
NDA203585_Response.R	Response analysis for potential effect of BAS-based dosing with data set of Analysis CML-300	Reviews\Ongoing PM Reviews\Omacetaxine_NDA203585_JEL\ER Analyses

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/s/

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09/06/2012

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09/06/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: **203585**	Submission Date(s): **3/30/12 (000), 6/14/12 (014), 6/21/12 (015), 7/24/12 (022)**
Brand Name	**To Be Determined**
Generic Name	**omacetaxine mepesuccinate**
Reviewer	**Joseph Grillo, Pharm.D.**
Acting Team Leader	**Bahru Habtemariam, Pharm.D.**
PM Reviewer	**Jee Eun Lee, Ph.D.**
PM Team Leader	**Kevin Krudys, Ph.D.**
OCPB Division	**DCP-5**
ORM division	**OND/ OHOP/DHP**
Sponsor	**Cephalon Inc.**
Relevant IND(s)	**062384**
Submission Type; Code	**Original NDA; 000 (SDN 1)**
Formulation; Strength(s)	**3.5 mg Lyophilized Powder in a Single-Use Vial**
Indication	**The treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI)**

Table of Contents

1 EXECUTIVE SUMMARY

Omacetaxine mepesuccinate acts as a non-specific, reversible inhibitor for protein elongation. The applicant is currently evaluating this drug for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI).

Omacetaxine mepesuccinate was originally reviewed by the office of clinical pharmacology (OCP) under NDA 22-374 which received a complete response (CR) action on 04/08/2010, and was subsequently withdrawn on 02/07/2011. In the current submission, the applicant addressed the OCP deficiencies noted in the CR letter.

The proposed induction dose is 1.25 mg/m^2 administered by SC injection twice daily for 14 consecutive days of a 28-day cycle. This is followed by the proposed maintenance dose of 1.25 mg/m^2 administered SC twice daily for 7 consecutive days of a 28-day cycle. Dose selection was based on literature data; there was no internal sponsor data to establish dose or exposure-response relationships. To support the proposed indication, the sponsor conducted two open-label, single-arm, trials in adult patients with Ph+ CML-CP, AP, or BP with either failure to prior imatinib therapy (CML-202) or with ≥ 2 prior TKIs (CML-202)and with loss of hematologic or cytogenetic response on current or most recent therapy. The combined results from these two trials report increased major cytogenetic response (MCyR) complete hematologic response (CHR) and duration in the target populations. The most common adverse reactions were bone marrow suppression, diarrhea, nausea, fatigue, asthenia, and injection site reaction.

The dosing regimen selection was based on literature data. The pharmacometrics reviewer's analysis of the proposed dose will be posted as a separate review at a later date.

Omacetaxine is primarily hydrolyzed to the inactive 4'-DMHHT metabolite via plasma esterases with little hepatic involvement. The major elimination route of omacetaxine is unknown, but will be evaluated postmarketing. The mean half-life of omacetaxine and 4'-DMHHT following SC administration is approximately 6 hours and 16 hrs, respectively.. Omacetaxine is a substrate of P-glycoprotein (P-gp). Omacetaxine and 4'-DMHHT do not inhibit or induce major cytochrome P-450 enzymes (CYPs) or P-glycoprotein (P-gp).

1.1 Recommendation

From a clinical pharmacology perspective, this NDA application is acceptable provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert and the applicant commits to the following post marketing requirement addressing clinical pharmacology related safety concerns with omacetaxine treatment.

1.2 Post Marketing Requirements

1.2.1 Conduct a mass balance trial in humans to determine the disposition and elimination pathways as well as to characterize the major metabolites of omacetaxine following subcutaneous injection. Depending on the results, hepatic and/or renal impairment trials may be required.

Protocol submission Date: Draft protocol was submitted on 07/31/2012
Trial Completion Date: September 2014
Final Trial Report: February 2015

1.3 Post Marketing Commitment

None

1.4 Comments to the Applicants

1.4.1 Conduct an in vitro induction study using human hepatocytes from at least three donors to evaluate the effects of omacetaxine and its 4'-DMHHT metabolite on the three inducible forms of cytochrome P450 (CYP1A2, CYP2B6, and CYP3A4) at relevant concentrations that minimize the culture toxicity experienced previously. The changes in the mRNA level of the target gene should be used as an endpoint as outlined in the Agency's 2011 draft guidance "Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations" (http://1.usa.gov/yaOuKn).

1.5 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings from the original review of NDA 22-374 and new information submitted under 203585

Omacetaxine mepesuccinate is a semi-synthetic alkaloid from Cephalotaxus fortunei (Chinese evergreen) that acts as a non-specific, reversible inhibitor for protein elongation. The applicant is currently evaluating this drug for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI).

Omacetaxine mepesuccinate was originally reviewed by OCP under NDA 22-374 which received a CR action on 04/08/2010, and was subsequently withdrawn on 02/07/2011. CP deficiencies were to 1) Reduce the vial size from 5 mg to 3.5 mg, 2) Conduct a mass balance trial in humans, 3) Conduct an in vitro CYP IND study (3+ donors), 4) Conduct an in vitro P-gp Inhibition study, 5) Repeat in vitro protein binding study, and 6) Explore the optimal dosing regimen in the ongoing and future trials. The applicant addressed these by proposing a new vial size, conducting three new in vitro trials, and submitting a protocol for a mass balance trial on 7/31/12. The applicant also submitted two exploratory analyses of the potential impact of intrinsic factor covariates by subgroup and an evaluation the concentration-QTc relationship using data from their CGX-635-205 trial. The applicant states that it has not begun additional trials with omacetaxine so dosing regimen optimization has not been further evaluated at this time.

Omacetaxine for injection is a lyophilized powder containing 3.5 mg of omacetaxine and 10 mg of mannitol in a clear 8-mL glass vial. The powder is reconstituted with 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP), prior to administration by SC injection. The proposed induction dose is 1.25 mg/m^2 administered by SC injection twice daily for 14 consecutive days of a 28-day cycle (Repeat cycles every 28 days until patients achieve a hematologic response). This is followed by the proposed maintenance dose of 1.25 mg/m^2 administered by SC injection twice daily for 7 consecutive days of a 28-day cycle (Treatment should continue as long as patients are benefiting from therapy).

To support the proposed indication, the sponsor conducted two open-label, single-arm trials in adult patients with Ph+ CML-CP, AP, or BP with either failure to prior imatinib therapy (CML-202) or with ≥ 2 prior TKIs (CML-202)and with loss of hematologic or cytogenetic response on current or most recent therapy. The combined results from these two trials report that 18% of chronic phase (CML-CP) patients achieved the primary endpoint of major cytogenetic response (MCyR) with a median duration of 12.5 months,

and 14% of accelerated phase (CML-AP) patients achieved the primary endpoint of complete hematologic response (CHR) with a median duration of 4.7 months. The most common adverse reactions were thrombocytopenia, anemia, neutropenia, diarrhea, nausea, fatigue, leukopenia, asthenia, injection site reaction, and lymphopenia.

The dosing regimen selection was based on literature data; drug development did not establish exposure-response relationships. The pharmacometrics reviewer's analysis of the proposed dose will be posted as a separate review at a later date.

Study CGX-635-205 is the only applicant-sponsored clinical pharmacology study to evaluate single- and multiple-dose PK as well as QTc interval prolongation of omacetaxine in 21 cancer patients. Peak concentrations of omacetaxine are reached 0.5-1 hour after SC injection of Omacetaxine. Omacetaxine has a mean±SD steady-state volume of distribution of approximately 141±93.4 L following SC administration for 11 days. The plasma protein binding of omacetaxine is less than or equal to 50%. Omacetaxine is primarily hydrolyzed to the inactive 4'-DMHHT metabolite via plasma esterases with little hepatic microsomal oxidative and/or esterase-mediated metabolism in vitro. The major elimination route of omacetaxine is unknown, but will be evaluated post-market. The mean percentage of omacetaxine excreted unchanged in the urine is less than 15%. The mean half-life of omacetaxine and 4'-DMHHT following SC administration is approximately 6 hours and 16 hrs, respectively. The plasma AUC of DMHHT is approximately 13% of omacetaxine AUC. Compared to a single dose, the plasma exposure to omacetaxine at steady state increased 90% following SC injection BID. Inter-patient variability in omacetaxine AUC was 70%.

Omacetaxine is a substrate of P-glycoprotein (P-gp). Omacetaxine and 4'-DMHHT do not inhibit major cytochrome P-450 enzymes (CYPs) or P-glycoprotein (P-gp). The likelihood of Omacetaxine or 4'-DMHHT to induce CYP450 enzymes has not been determined conclusively.

No substantial QT-prolonging effects of omacetaxine were detected. However, QTc effects less than 10 ms could not be verified in the absence of placebo and positive controls.

Signatures

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2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song. In the current submission the applicant has proposed reducing the single use vial strength from 5 mg to 3.5 mg pursuant to FDA's deficiency comment in its 04/08/2010 action letter. The FDA stated that the proposed 5 mg single use vial contained more than twice the average dose of omacetaxine used in the efficacy and safety studies and that this degree of overfill carried significant potential risk for overdose as well as the environmental impact of drug disposal. The reviewer finds this reduction in the single use vial strength from 5 mg to 3.5 mg acceptable from a Clinical Pharmacology perspective.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

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? (If yes, refer to 2.6, Analytical Section; if no, describe the reasons.)

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.2.4.3 Does this drug prolong the QT or QTc interval?

See 03/25/2010 Clinical Pharmacology review by Dr. Pengfei Song and the 12/15/2009 QT-IRT consult review of NDA 22-374.

Based on the QT -IRT review of NDA 22-374, no substantial QT-prolonging effects of omacetaxine were detected. However, QTc effects less than 10 ms could not be verified in the absence of placebo and positive controls. At that time the QT -IRT recommend the following labeling:

(b) (4)

In the current submission the applicant also provides an exploratory graphic evaluation of time-matched QTcB and QTcF values versus omacetaxine concentration to evaluate the concentration-QTc relationship. The QT -IRT reviewed this new information and finds that there is no new evidence or data to change the overall conclusions noted in the previous review of NDA 22-374 9/4/2012. The clinical pharmacology reviewer agrees with the QT –IRT conclusion and proposed labeling.

2.2.4.4 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?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song. The pharmacometrics reviewer's analysis of the proposed dose from the current submission will be posted as a separate review at a later date.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters? (Provide tables to refer to in subsequent questions in this section.)

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.2.5.3 What are the characteristics of drug absorption? (This may include discussion of transporter or pH effect.)

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.2.5.4 What are the characteristics of drug distribution? (Include protein binding.)

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

The Agency's 04/08/2010 complete response letter for NDA 22-374 cited a deficiency that the applicant should conduct an additional in vitro study to determine the plasma protein binding of omacetaxine. The study provided in the NDA 22-374 submission was deemed inconclusive due to substantial negative values reported. The clinical pharmacology reviewer stated this suggested a lack of equilibrium at the end of sampling or a problem with the bioanalytical method.

In the current submission the applicant addresses this deficiency by assessing the extent of omacetaxine binding to plasma proteins using ultrafiltration in the presence and absence of paraoxon. Omacetaxine recovery following incubation for 30 minutes was greater than 92.2%. The median percentage of protein binding of omacetaxine at concentrations 1.0, 2.5, 5.0, and 7.5 μM[1] ranged from 37% to 50% [no paraoxon]and 22% to 41% [no paraoxon]. The positive control, warfarin, demonstrated 99.4% protein binding when subjected to the same conditions as omacetaxine. The percentage of protein binding of omacetaxine did not appear concentration dependent. Three negative values were reported but did not significantly affect the overall results as in the previous study. The reviewer finds these results acceptable and the approved labeling should state that the percentage of protein binding of Omacetaxine is less than or equal to 50%. No protein binding related precautionary measures are required.

Studies evaluating the relative distribution to different plasma proteins (eg, alpha1- acid glycoprotein [AGP] versus albumin) were not conducted. Given the above results this is acceptable at this time.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination? (This may include table with results of mass balance study.)

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

A mass balance study of omacetaxine administered by SC injection in humans has not been conducted. This issue was sent to the applicant in the Agency's 04/08/2010 complete response letter for NDA 22-374. The applicant submitted a draft protocol to the Agency for a human mass balance trial on 7/31/12 with a timeline to submit a final study report in February 2015. The Agency provided comments to the applicant regarding its draft protocol on 8/31/2012. The reviewer finds this protocol acceptable, provided the agency's comment to revise the inclusion criteria to only include patients with normal to mild hepatic dysfunction as defined by the National Cancer Institute Organ Dysfunction Working Group Criteria Total bilirubin (≤ 1.5 x ULN) or Child Pugh Score A and 2) Normal to Mild renal impairment (eGFR or CrCl ≥ 60 mL/min) is addressed. This trial should be conducted under a PMR. The need for additional organ impairment studies should be addressed as part of the review of this PMR.

2.2.5.6 What are the characteristics of drug metabolism? (This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug.)

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.2.5.7 What are the characteristics of drug excretion?

[1] Following 30 minutes incubation in human plasma in the presence or absence of paraoxon (to prevent hydrolysis by plasma esterases).

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

The applicant also submitted an exploratory analysis of the potential impact of intrinsic factor covariates by subgroup analyses. The pharmacometrics reviewer's assessment this exploratory analysis will be posted as a separate review at a later date.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song. The pharmacometrics reviewer's assessment of the exploratory analysis from the current submission addressing this issue will be posted as a separate review at a later date.

2.3.2.1 Elderly

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song. The pharmacometrics reviewer's assessment of the exploratory analysis from the current submission addressing this issue will be posted as a separate review at a later date.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.3.2.3 Gender

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song. The pharmacometrics reviewer's assessment of the exploratory analysis from the current submission addressing this issue will be posted as a separate review at a later date.

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.3.2.5 Body Weight

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei. The pharmacometrics reviewer's assessment of the exploratory analysis from the current submission addressing this issue will be posted as a separate review at a later date.

2.3.2.6 Renal impairment

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song. The pharmacometrics reviewer's assessment of the exploratory analysis from the current submission addressing this issue will be posted as a separate review at a later date.

2.3.2.7 Hepatic impairment

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song. The pharmacometrics reviewer's assessment of the exploratory analysis from the current submission addressing this issue will be posted as a separate review at a later date.

2.3.2.8 What pharmacogenetics information is there in the application and is it important or not

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.3.2.9 What pregnancy and lactation use information is there in the application?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.3.2.10 Other human factors that are important to understanding the drug's efficacy and safety

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.4.1.1 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

The Agency's 04/08/2010 complete response letter for NDA 22-374 cited a deficiency that the applicant should conduct an in vitro induction study using human hepatocytes from at least three donors to valuate the effects of omacetaxine on the three inducible forms of cytochrome P450 (CYP1A2, CYP2B6, and CYP3A4). The study provided in the NDA 22-374 submission was deemed inconclusive as the study was conducted with human hepatocytes from only one donor.

In the current submission the applicant addresses this deficiency by conducting an in vitro study assessing the effect of treating primary cultures of fresh human hepatocytes (3 donors) for three days with a control (DMSO, 0.1% v/v), omacetaxine (0.025, 0.25, 1, 2.5 or 25 µM) or one of three accepted positive controls human CYP inducers[2] on cytochrome P450 (CYP) enzymes CYP1A2, CYP2B6, and CYP3A4 activity. The applicant's activity endpoint is acceptable, in this case, given it was recommended in FDA's previous drug interaction guidance for in vitro induction studies. The current revised draft guidance recommends that the changes in the mRNA level of the target gene should be used as the endpoint.

Cellular toxicity was reported in the first incubation preparation, as evidenced by release of lactate dehydrogenase (LDH) from the cells and by morphologic changes in the cells. For the 2 subsequent hepatocyte cultures, the incubation time was reduced by 1 day and concentrations were also reduced to 0.025-1.0 µM. Evidence of concentration-related toxicity was also observed in these cells, although less markedly. Following treatment with 0.025 to 25 µM of omacetaxine, a global concentration-dependent decline in CYP activities was observed mostly likely a result of cellular toxicity. While the applicant interprets these data as indicating omacetaxine appears not to be an inducer of CYP1A2, CYP2B6, or CYP3A4 at concentrations of 0.025-25 µM, the reviewer finds these the results inconclusive due to the omacetaxine related toxicity noted in the cell culture. The reviewer recommends these data not be communicated in the approved product label. A comment should be sent to the applicant suggesting that this issue should be further explored using the revised methodology from FDA's current draft guidance to overcome the cofounding effect of cellular toxicity noted in the current study.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

The Agency's 04/08/2010 complete response letter for NDA 22-374 cited a deficiency that the applicant should conduct an in vitro study to determine if omacetaxine is an inhibitor of P-glycoprotein. This issue was not evaluated in the NDA 22-374 submission.

In the current submission the applicant addresses this deficiency by conducting an in vitro study assessing the ability of omacetaxine or its primary metabolite, 4'-DMHHT, over a concentration range of 0.1-50 µM to inhibit the P-glycoprotein-mediated efflux of the P-glycoprotein substrate loperimide in MDR1-MDCK cells. IC_{50} values were not obtained over the concentration range studied because sufficient inhibition was not observed. The maximum inhibition observed was 30% and 16% for omacetaxine and 4'-DMHHT, respectively. The positive control inhibitors, cyclosporine A and ketoconazole, were

[2] Omeprazole[CYP1A2](100 µM), Phenobarbital [CYP2B6] (750 µM) and rifampin [CYP3A4] (10 µM)

found to be moderate inhibitors of the P-gp mediated efflux of loperamide in MDR1-MDCK cells with IC_{50} ± SE of 1.1 ± 0.2 μM and 1.1 ± 0.3 μM, respectively.

The methods are acceptable although loperimide is not a probe substrate currently recommended in FDA's new draft drug interaction guidance. Given the concentrations following 1.25 mg/m^2 SC doses over a 2-week period averaged 36.2 ng/mL (0.066 μM) in clinical trials, the concentration range is also deemed acceptable. Based on the above findings, the reviewer agrees with the applicant's conclusion that omacetaxine and 4'-DMHHT are unlikely inhibitors P-glycoprotein-mediated efflux at concentrations of 50 μM or below and additional in vivo studies are not required at this time. The approved labeling should reflect these in vitro findings in the clinical pharmacology section.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

None

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

In the current submission that includes the proposed 3.5 mg vial strength, the applicant states that "Despite a change in the formulation of omacetaxine mepesuccinate for injection that occurred between production of the formulation used for the clinical studies supporting this application and that of the commercial product, no bioavailability, comparative bioavailability, or bioequivalence studies were deemed necessary." This issue will be reviewed by ONDQA per memorandum of understanding with OCP.

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.5.4 When would a fed BE study be appropriate and was one conducted?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

2.6 Analytical Section

See 03/25/2010 Clinical Pharmacology review of NDA 22-374 by Dr. Pengfei Song.

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/s/

JOSEPH A GRILLO
09/06/2012

BAHRU A HABTEMARIAM
09/06/2012

NAM ATIQUR RAHMAN
09/06/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203-585	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	March 30, 2012		
Division:	Division of Hematology Products	**Team Leader:** Angelica Dorantes, PhD	
Applicant:	Cephalon, Inc.	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	TBD	**Date Assigned:**	April 3, 2012
Established Name:	Omacetaxine mepesuccinate for Injection	**Date of Review:**	September 4, 2012
Indication:	Treatment of chronic or accelerated phase chronic myeloid leukemia (CML)	**Type of Submission:** Original New Drug Application – 505(b)(1)	
Dosage form/ strengths	Lyophilized Powder for Injection/ 3.5 mg/vial		
Route of Administration	Subcutaneous Injection		
Type of Review:	Biowaiver Request		

SUBMISSION:

The proposed drug product is a lyophilized powder for injection containing omacetaxine mepesuccinate as the active ingredient and mannitol as the inactive ingredient. Omacetaxine mepesuccinate is a protein synthesis inhibitor indicated for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to prior tyrosine kinase inhibitors (TKI). The drug product is a lyophilized powder that is reconstituted with 1.0 mL 0.9% sodium chloride immediately prior to subcutaneous injection. At a dose of 1.25 mg/m^2 twice daily. This application is an electronic NDA, filed as a 505(b)(1) application. The clinical formulation and commercial formulation are different as shown in Table 1 below. The clinical formulation and commercial formulation should be linked by a BE study or a Biowaiver request should be submitted. The original NDA did not contain a BE study or a Biowaiver request. In response to an information request (IR) dated 5/10/12, a Biowaiver request was submitted in an amendment to the NDA dated 5/21/12. This review is focused on the evaluation of the Biowaiver request.

BIOPHARMACEUTIC INFORMATION:

The clinical formulation strength (5 mg omacetaxine mepesuccinate /vial) was changed to the commercial formulation strength (3.5 mg omacetaxine mepesuccinate /vial) upon request by the Agency to reduce the risk of overdose as well as to reduce the environmental impact, as shown in Table 1:

Table 1: Prelyophilization Composition of Omacetaxine Mepesuccinate for Injection Solution

Ingredient	Amount per vial	
	Clinical formulation	Commercial formulation
Omacetaxine mepesuccinate	5 mg	3.5 mg
Mannitol		(b) (4)
		(b) (4)

q.s.=quantum satis (ie, a sufficient quantity).

In the amendment dated 5/21/12, the Applicant requested a waiver of the *in vivo* bioequivalence study requirement as allowed under 21 CFR 320.22(e), because the Applicant believes that the in vivo bioavailability is self-evident due to the high solubility and rapid absorption of the drug product. Moreover, the Applicant claims that the drug product's indication is for a targeted patient population with a life-threatening disease with no approved therapeutic alternatives and thereby meets the requirement of needed protection of the public health.

Assessment of Biowaiver Request

(b) (4) the concentration of the active ingredient (omacetaxine mepesuccinate) will be lower in the commercial formulation (3.5 mg/mL) compared to the clinical formulation (5 mg/mL). Thus, when keeping the dose (1.25 mg/m^2 twice daily) the same, a larger volume of the commercial formulation will be injected subcutaneously compared to the clinical formulation. The Applicant was sent the following IR on 8/15/12:

Since for your proposed commercial formulation the volume of the injectable solution will be different than that of the clinical trial formulation (to obtain the same dose), provide a justification with data demonstrating that the volume (ml) of the injectable solution does not have any impact on the bioavailability of omacetaxine mepesuccinate administered subcutaneously.

The Applicant responded on 8/22/12 as follows:

The concentration of reconstituted omacetaxine mepesuccinate was reduced from 5 mg/mL during clinical trials to 3.5 mg/mL for the commercial presentation. The decrease of the vial content from 5 mg to 3.5 mg was requested in the Complete Response, dated April 8, 2010, of the initial NDA 022-374. The reconstitution volume remained fixed at 1 mL normal saline. The 3.5 mg/mL solution was dosed at 0.36 mL/m^2 versus the 5 mg/mL solution which will be dosed at 0.25 mL/m^2 (equivalent to 1.25 mg/m^2). As an example, a patient with a body surface area (BSA) of 1.86 m^2, which corresponds to the mean and median BSA of patients included in the clinical program (studies CML-202, CML-203, and 04.2/04.3 patients) will receive a slightly larger dose using the commercial formulation by a difference in dose volume of 0.2 mL (0.67 mL versus 0.47 mL for the 3.5 mg and 5.0 mg vials, respectively). We believe that this difference will still have no impact on the pharmacokinetics, safety and efficacy of the product. This is further supported

by the fact that the solubility of omacetaxine mepesuccinate is 70 mg/mL at pH 7.4 which is considered highly soluble. As described in section 2.7.2.3.3.1 of NDA 203-585, omacetaxine mepesuccinate has been demonstrated to be rapidly absorbed with maximum concentrations measured as early as 30 minutes (the first sampling time point) following subcutaneous administration. In a cross-study comparison of systemic exposure following intravenous and subcutaneous administrations of omacetaxine mepesuccinate, the bioavailability following subcutaneous administration is high (approximately 70%-90%; study CGX-635-205 and Savarej et. al., 1986). This further supports that the change in the concentration and volume of the injectable solution will not likely produce a difference in bioavailability.

Evaluation of Applicant's Response:

An average sized person will receive a subcutaneously injectable volume of 0.67 mL of the commercial formulation instead of 0.47 mL of the clinical formulation. Due to the high solubility (70 mg/mL at pH 7.4) and high (70-90%) bioavailability following subcutaneous administration, it is unlikely that this difference of about 0.2 mL in injectable volume will affect the bioavailability of the drug. In addition, from the clinical perspective (per e-mail from the Medical Reviewer, Firoozeh Alvandi, MD), there should not be a significant difference in safety and/or efficacy based on the difference in injectable volume. Therefore, the Applicant's request for a Biowaiver for their proposed drug product, omacetaxine mepesuccinate for Injection, is acceptable and the Biowaiver is granted based on 21 CFR 320.22(b). Note that the acceptance of the biowaiver is not based on 21 CFR 320.22(e) as the Applicant requested.

RECOMMENDATION:

A waiver of the *in vivo* bioequivalence study requirement is granted. From the Biopharmaceutics perspective, NDA 203-585 for omacetaxine mepesuccinate for Injection (3.5 mg/vial) is recommended for APPROVAL.

Signature	**Signature**
Elsbeth Chikhale, Ph.D.	Angelica Dorantes, Ph.D.
Biopharmaceutics Reviewer	Biopharmaceutics Team Leader
Office of New Drug Quality Assessment	Office of New Drug Quality Assessment

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/s/

ELSBETH G CHIKHALE
09/04/2012

ANGELICA DORANTES
09/04/2012

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

NDA/BLA Number:	203585	**SDN:**	1
Sponsor:	Cephalon Inc.	**Date of Submission**	3/30/12
Brand Name:	Omasona	**Generic Name:**	omacetaxine mepesuccinate
Drug Class:	Reversible inhibitor of protein synthesis		
Dosage Form:	Single-use vial containing 3.5 mg of omacetaxine mepesuccinate as lyophilized powder for injection		
Dosing Regimen:	• Induction Dose: 1.25 mg/m² SC twice daily for 14 consecutive days of a 28-day cycle. Repeat cycles every 28 days until patients achieve a hematologic response. • Maintenance Dose: 1.25 mg/m² SC twice daily for 7 consecutive days of a 28-day cycle. Treatment should continue as long as patients are benefiting from therapy.		
Route of Administration:	Subcutaneous injection		
Indication:	Treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to prior tyrosine kinase inhibitors (TKI) including imatinib, dasatinib or nilotinib		
OCP Division:	DCP5	**OND Division:**	DHP
OCP Reviewer:	Joseph Grillo, Pharm.D.		
OCP Team Leader:	Julie Bullock, Pharm. D.		
PM Reviewer:	TBD		
PM Team Leader:	Christine Garnett, Pharm.D.		
GG Reviewer:	Rosane Charlab Orbach		
GG Team Leader:	Issam Zineh		
Priority Classification:	☒ Standard ☐ Priority	**PDUFA Due Date**	1/30/12
OCP Review Due Date:	11/22/12	**OND Division Due Date:**	12/5/12

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Critical Comments
Table of Contents present and sufficient to locate reports, tables, data, etc.	☒		
Tabular Listing of All Human Studies	☒		
Human PK Summary	☒		New studies ptx029 & ptx027 not incorporated into summary
Labeling	☒		
Bioanalytical and Analytical Methods	☒		
I. Clinical Pharmacology			
Mass balance:	☐		Sponsor previously submitted hardcopy protocol summary & timeline to address deficiency (not reviewed by OCP)
Isozyme characterization:	☒	2	plasma & liver microsomes
Blood/plasma ratio:	☐		
Plasma protein binding:	☒	3	New study submitted to address previous deficiency
Transporters	☒	1	In vitro permeability
Pharmacokinetics (e.g., Phase I) -			
Healthy Volunteers:			
single dose:	☐		
multiple dose:	☐		
Patients:			
single dose:	☒		
multiple dose:	☒	1	Raw data not submitted (was submitted in NDA 22374)
Dose proportionality -			Applicant proposal based on published literature report

fasting / non-fasting single dose:	☐		
fasting / non-fasting multiple dose:	☐		
Drug-drug interaction studies -			
In-vivo effects on primary drug:	☐		
In-vivo effects of primary drug:	☐		
Concomitant therapy:	☐		
In-vitro:	☒	3	CYP INH/IND CYP IND (to address previous deficiency) P-gp INH (to address previous deficiency)
Subpopulation studies -			
ethnicity:	☒		
gender:	☒		
pediatrics:	☐		
geriatrics:	☒	1	Pop-PK report Small sample size for renal or hepatic impairment groups
Body weight/BSA:	☒		
renal impairment:	☒		
hepatic impairment:	☒		
PD -			
Phase 2:	☐		
Phase 3:	☐		
PK/PD -			
Phase 1/2, proof of concept:	☒	2	P2 pivotal trials (CML-202 & -203) state plasma for HHT levels collected but no PK analysis
Phase 3 clinical trial:	☐		
Population Analyses -			
Data rich:	☒		
Data sparse:	☐		
QT evaluation:	☒	1	Pop-PK report
II. Biopharmaceutics			
Absolute bioavailability:	☐		
Relative bioavailability -			
solution as reference:	☐		
alternate formulation as reference:	☐		
Bioequivalence studies -			
traditional design:	☐		
replicate design:	☐		
Food-drug interaction studies:	☐		
Bio-waiver request based on BCS	☐		
BCS class	☐	1	In vitro permeability
Alcohol induced dose-dumping	☐		
III. Other CPB Studies			
Genotype/phenotype studies	☐		
Chronopharmacokinetics	☐		
Pediatric development plan	☐		
Literature References	☒	3	Levy 2006; Savaraj 1987; and Savaraj 1986
Total Number of Studies		18	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		X		
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			Tolerability
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			New studies Ptx 027 & 029 Not included in CP summary
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			Some links incorrect
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		• Need raw data for CGX-205 (submitted in previous NDA) • Need PK data from trials CML-202 & -203
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?		X		Only minimal data were submitted
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		Pop-PK analysis to evaluate covariates submitted
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		X		Waiver requested
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X		

17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		X		
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

Is the Clinical Pharmacology Section of the Application Fileable?

☒ **Yes**

☐ **No**

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

N/A

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

- Provide raw data for trial CGX-205 as SAS transport files (.xtp). In addition to concentration-time and derived PK parameter datasets domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. It appears these files were submitted for trial CGX-205 in the previous NDA 22-374 (now withdrawn). Resubmitting these files to NDA 203-585 would address this request for CGX-205. This information should be provided within 10 business days.
- We note your study reports for CML-202 and CML-203 state that PK sampling was conducted. Provide the raw data for this sampling as Pharmacokinetic Concentrations (PC) and Pharmacokinetic Parameters (PP) domains to the data already submitted in CDISC format for these trials. This information should be provided within 10 business days.
- Incorporate the information from the newly submitted studies ptx029 & ptx027 into relevant sections of the clinical pharmacology summary. These studies were conducted in response to deficiencies noted by the Agency regarding NDA 22-374 (now withdrawn) in its 4/8/2010 complete response letter. The applicant should also justify how these new studies addressed the agencies concerns in the revised clinical pharmacology summary. A revised clinical pharmacology summary should be provided within 10 business days.
- We note that the hyperlink to study cln003 in the clinical pharmacology summary (Section 1.2.1) links to an incorrect study report (cln013). The applicant should carefully review the clinical pharmacology and biopharmaceutical summaries and correct any broken hyperlinks within 10 business days.
- The protocol summary for the mass balance study (C41443/1103), submitted to IND 62,384 on 12/20/11, does not contain sufficient detail for the Agency to make a decision regarding whether it will adequately addresses the significant deficiency noted by the Agency regarding NDA 22-374 (now withdrawn) in its 4/8/2010 complete response letter. If the applicant is proposing to start enrollment in February 2013, it should submit the full protocol to the IND 62,384 as soon as possible. We remind the applicant that, to avoid substantial confounding, a mass balance trial should be conducted in subjects or

patients with normal hepatic and renal function. Your current proposal appears to include patients with mild to moderate hepatic or renal impairment. Please provide a timeline for submitting the full protocol with 5 business days.

Signatures:

Joseph Grillo, Pharm.D. Reviewer Division of Clinical Pharmacology 5	Julie M. Bullock, Pharm.D. Team Leader Division of Clinical Pharmacology 5

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH A GRILLO
05/10/2012

JULIE M BULLOCK
05/11/2012