CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203585Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203585/0
Priority or Standard	Priority
Submit Date(s)	March 30, 2012
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Division / Office	Division of Hematology Products Office of Hematology Oncology Products
Reviewer Name(s)	Firoozeh Alvandi, MD
Review Completion Date	September 02 , 2012
Established Name	Omacetaxine mepesuccinate
(Proposed) Trade Name	Synribo
Therapeutic Class	Cephalotaxine
Applicant	Cephalon, Inc.
Formulation(s)	Lyophilized powder for reconstitution
Dosing Regimen	Induction: Subcutaneous Injection 1.25 mg/^{2} dose twice daily for 14 consecutive days every 28 days over a 28-day cycle Maintenance: Subcutaneous Injection 1.25 mg/^{2} dose twice daily for 7 consecutive days every 28 days over a 28-day cycle
Indication(s)	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 (TKIs)
Intended Population(s)	Patients with accelerated or chronic phase CML (CML-AP or CML-CP)

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based upon my review of the data submitted in support of this NDA, the recommended regulatory action is accelerated approval of omacetaxine mepesuccinate (subsequently referred to in this review as omacetaxine) as third line therapy for the treatment of accelerated or chronic phase chronic myelogenous leukemia (CML), by subcutaneous route of administration. Accelerated, and not regular, approval is recommended as the applicant has not provided the requisite 24 months of follow-up data that FDA expects for regular approval. The submission contained a median of 19.5 (range 14.4-23.1) and 11.5 (range 6.8-16) months of follow up data for the primary endpoints for CML-CP and CML-AP population, respectively. The recommendation for approval (accelerated) is based upon the results of the analysis of a subset of patients with CML-AP and CML-CP from two trials (for efficacy) CML-202 and CML-203, titled 'Analysis CML-300' and, for the safety analysis includes an additional trial CML4.2/4.3 in patients with CML-AP. These trials were single arm trials conducted in patients who have been intolerant or resistant to at least 2 prior TKIs, one of which must have been imatinib. The subset of patients selected from CML-202 and CML-300 for post hoc efficacy analysis (Analysis CML-300) consists of patients in both trials who received 2 or more approved tyrosine kinase inhibitors (TKIs) at a minimum, had evidence of resistance or intolerance to dasatinib and/or nilotinib.

The efficacy result for the primary endpoint of Major Cytogenetic Response (MCyR) (complete and partial cytogenetic response) for patients with CML-CP was 20.5% with median duration of response of 17.7 months (95% CI 4.1- N/A). Two patients with CML-CP had MCyR at trial entry. With removal of these patients from the efficacy analysis who had MCyR at trial entry, the primary end point of MCyR for patients with CML-CP was 18.4% with a median duration of 12.5 months (95% CI 3.5-NA).

The efficacy result for the primary endpoint of Major Hematologic Response (MaHR) (complete hematologic response and no evidence of leukemia) patients with CML-AP was 26.8% (14.2-42.9) with median duration of 9.0 months (3.6-14.1). Of the CML-CP patients in analysis 300, 24 patients (29.1%) entered the trial in a complete hematologic response (CHR). Of the CML-AP patients in analysis 300, 9 patients (22%) were in CHR at baseline. With removal of those patients from the efficacy analysis who had best response at trial entry, the primary end point of MaHR for patients with CML-AP was 14.3% with a median duration of 4.7 months (95% CI 3.6-NA). The efficacy results from this post-hoc subset analysis of two single-arm trials are adequate given the absence of any approved drug in the third line setting for treatment of CML. This analysis was agreed to by the FDA after the initial application received a CR letter.

Omacetaxine should be prepared and administered in the clinical setting, [redacted] (b) (4)

The most frequently reported adverse reactions (≥ 20%) associated with subcutaneous omacetaxine use include thrombocytopenia, anemia, diarrhea, nausea, fatigue/asthenia, febrile neutropenia, and pyrexia.

1.2 Risk Benefit Assessment

Omacetaxine has a positive risk:benefit assessment for patients with CML-CP or CML-AP who have previously received at least 2 prior TKIs. Omacetaxine has shown activity in both the accelerated and chronic phases of CML in the third line setting in patients who have been intolerant or resistant to at least 2 prior TKI drugs, and has an acceptable safety profile. Analysis of the safety results found 10% discontinuations due to treatment emergent adverse events TEAES in the CML-CP group and 11% in the CML-AP group. The drug is myelosuppressive with most grade 3-4 adverse events being of hematological nature (thrombocytopenia, anemia, and neutropenia) in both patient populations (CML-CP and CML-AP) and gastrointestinal adverse events with few of grade 3-4, and a low incidence of injection site reaction (mostly injection site erythema of grade 1-2).

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**Summary of Evidence:** CML is a hematopoietic stem cell disorder with approximately 10,000 new cases diagnosed annually in the US and Europe. CML has 3 phases, representing a disease continuum; i.e., chronic phase, accelerated phase, and blast phase. The disease is usually diagnosed in chronic phase and progresses to accelerated and then blast phase as the number of blasts in the blood and bone marrow increases. Before the approval of the TKI imatinib, the median survival of patients with CP-CML was 4-6 years. Survival after development of an AP and BP transformation was typically <1 year and only a few months respectively. In a 7-year follow-up analysis of the imatinib (IRIS) trial, the survival rate was 86%. Despite these improvements in CML treatment, approximately 30-40% of patients receiving imatinib discontinue treatment after 5-8 years	**Conclusions (implications for decision):** Omacetaxine has shown activity in the third line setting in this patient population for whom there is no available therapy.

	due to drug resistance or toxicity. There are now three other TKIs approved for CML; dasatinib, nilotinib, and bosutinib. However, none are approved for third-line CML. Patients with CML who have failed two prior TKIs have no available therapies. CML-CP and CML-AP resistant to or intolerant of therapy with at least 2 TKIs is a serious and life-threatening condition.	
Unmet Medical Need	**Summary of Evidence:** There are no approved therapies for patients with CP-CML or AP-CML after receipt of two prior TKIs.	**Conclusions (implications for decision):** There is a need for treatments for patients who have not responded satisfactorily to two approved therapies in the form of TKIs
Clinical Benefit	**Summary of Evidence:** Analysis CML-300 is a post-hoc analysis of a subset of patients from two single-arm trials (CML-202 and CML-203) who have received at least 2 prior TKIs (one must have been imatinib). The results of this analysis demonstrate clinical activity in this subset of patients. CML-CP: MCyR of 18.4% CML-AP: MaHR of 14.3%	**Conclusions (implications for decision):** The drug has shown activity in the intended patient population. The Agency has accepted data from single-arm CML trials with 24 months of follow-up as evidence of clinical benefit.
Risk	**Summary of Evidence:** Major common adverse events are hematological with thrombocytopenia being the most common. The other adverse events found in >20% of subjects were anemia, neutropenia, and GI adverse events of diarrhea and nausea, and fatigue/asthenia.	**Conclusions (implications for decision):** This is a myelosuppressive drug with additional GI toxicity. In light of the activity it has shown and the lack of other therapy available in the third line treatment of CML-CP and CML-AP, the risk is acceptable.
Risk Management	**Summary of Evidence:** Omacetaxine is myelosuppressive, has GI toxicities, and may cause hyperglycemia. These toxicities are managed by holding drug, instituting supportive care (transfusions, growth factors, antiemetics, and antihyperglycemic agents).	**Conclusions (implications for decision):** The applicant has included in the label acceptable management for these in the form of dose/cycle delays and standard management of hematologic and GI toxicities and has included in the label that patients with pre-existing diabetes should be closely monitored.
Benefit-Risk Summary and Assessment As patients with CML (CP and AP) who have received at least two prior TKIs have no available therapy, the risks associated with omacetaxine are acceptable.		

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No risk evaluation and mitigation strategies are recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

The submission being reviewed, on which accelerated approval is based, provided 19.5 and 11.5 months of follow up data for the CML-CP and CML-AP populations, respectively. The submission did not contain the requisite 24 months of follow-up data required for regular approval in this indication. Therefore, a total of 24 months of efficacy/safety follow-up data for each patient enrolled will be necessary to assess the results for conversion from an accelerated to regular approval. The Agency is requesting a PMR for 24-months follow up data to be submitted by the applicant.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Omacetaxine mepesuccinate

Chemical Class: New molecular entity.

Pharmacologic Class: Omacetaxine does not belong to an established pharmacologic class (EPC) at this time.

Applicant's Proposed Indication: "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.

Proposed Dosing Regimen:
Induction Dose: 1.25 mg/m^2 administered by subcutaneous injection 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/m^2 administered by subcutaneous injection twice daily for 7 consecutive days of a 28-day cycle. Treatment should continue as long as patients are benefiting from therapy.

Mechanism of Action: The mechanism of action of Omacetaxine has not been fully elucidated but includes inhibition of protein synthesis. Omacetaxine binds to the A-site cleft in the peptidyl-transferase center of the large ribosomal subunit, from the Haloarcula marismortui archaea bacteria, which is expected to block polypeptide chain elongation.

It is a semisynthetic form of a plant alkaloid extract from the Chinese evergreen *Cephalotaxus fortunei.* The chemical name for omacetaxine mepesuccinate is cephalotaxine, 4′-methyl (2′R)-hydroxyl-2′-(4″-hydroxyl-4″-methylpentyl) butanedioate (ester), [3(R)].

Omacetaxine has been under investigation in the US, Europe and China for over 20 years, with the initial U.S. IND submitted by the National Cancer Institute (NCI) in 1981. However, the intravenous drug was associated with cardiac toxicities, consisting of hypotension and arrhythmias, which were subsequently ameliorated with use of lower doses and modifications to the administration of the drug. With the development of imatinib and other TKIs, further development of the drug was delayed.

2.2 Tables of Currently Available Treatments for Proposed Indications

Chronic myeloid leukemia (CML) results from the neoplastic transformation of a hematopoietic stem cell, affecting all hematopoietic cell lineages. CML is characterized by the presence of the Philadelphia chromosome, (a reciprocal translocation between the long arms of chromosomes 9 and 22, leading to formation of a Bcr-Abl gene). The product of this translocation, Bcr-Abl protein, is a constitutively active tyrosine kinase that causes the abnormal myelopoiesis in CML. There are three phases in CML: an initial chronic phase (CP), an accelerated phase (AP), and a final blast crisis or acute leukemic phase (BP). Transition from CP to AP and BP usually occurs gradually over a period of one or more years, but a blast crisis may occur more rapidly.

Current available treatment options for CML are listed in Table 1, below.

Table 1 Currently Available Treatment for Chronic Myeloid Leukemia

Drug	Labeled CML Indications
Imatinib (Gleevec) [Novartis]	1. Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myelogenous leukemia (Ph+CML) in chronic phase. 2. Patients with Philadelphia chromosome positive (Ph+CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy.
Nilotinib (Tasigna) [Novartis]	1. The treatment of newly diagnosed patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+CML) in chronic phase. 2. The treatment of chronic phase (CP) and accelerated phase (AP) Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib.
Dasatinib (Sprycel) [BMS]	1. Newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. 2. Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
Bosutinib (Bosulif) [Pfizer]	1. The treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy.
Cytarabine	Blast phase of chronic myelocytic leukemia
Interferon-2a (Roferon-A)	For chronic phase, Philadelphia chromosome (Ph) positive chronic myelogenous leukemia (CML) patients who are minimally pretreated (within 1 year of diagnosis).

Table 2 Currently Available Treatment for Chronic Myeloid Leukemia by Phase

CML Phase	First Line	Resistant/Intolerant After Imatinib	After Failure of IFN
Chronic Phase (CP)	Interferon 2-A Imatinib Nilotinib (AA)* Dasatinib (AA)*	Nilotinib Dasatinib Bosutinib	Imatinib
Accelerated Phase (AP)		Nilotinib Dasatinib Bosutinib	Imatinib
Blast Crisis (BC)	Cytarabine	Dasatinib Bosutinib	Imatinib

* AA= Accelerated approval

Although interferon has regular approval for patients with chronic phase CML who are minimally pre-treated, imatinib, dasatinib, and nilotinib are the standard care for CP-CML. Imatinib, nilotinib, and dasatinib all have Category 1 recommendations in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for front line Philadelphia Chromosome positive CML. Interferon is rarely utilized due to associated toxicities and is of historical interest only.

Although cytarabine has regular approval for blast phase CML, the tyrosine kinase inhibitors are often used in combination with AML-type induction chemotherapy or alone followed by hematopoietic stem cell transplantation.

There is currently no product with an indication for treatment of CML-CP or CML-AP after two prior TKIs.

2.3 Availability of Proposed Active Ingredient in the United States

Not available as this is a new molecular entity.

2.4 Important Safety Issues With Consideration to Related Drugs

This is a new molecular entity (NME) that has not been assigned a specific class and there are no other known related drugs to the NME, omacetaxine.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

NDA 22-374 was submitted by ChemGenex [the previous Sponsor] in November 2009 seeking approval for omacetaxine (with the proposed trade name of Omapro, at the time) for treatment of patients with chronic myeloid leukemia who have failed therapy with imatinib and had the Bcr-Abl T315I mutation.

Data from two trials (CML-202 and CML-203) was submitted in support of that NDA. Trial CML-202 enrolled 103 patients with CML chronic phase (CP), accelerated phase (AP) and blast phase (BP). It was a phase 2 open-label trial of the subcutaneous administration of homoharringtonine (omacetaxine) (CGX-635) in the treatment of patients with Chronic Myeloid Leukemia (CML) with the T315I Bcr-Abl gene mutation. Trial CML-203 enrolled 100 patients with CML chronic phase (CP), accelerated phase (AP) and blast phase (BP). It was a phase 2 open-label trial of the subcutaneous administration of homoharringtonine (omacetaxine) (CGX-635) in the treatment of patients with Chronic Myeloid Leukemia (CML) who were resistant to or intolerant of prior tyrosine kinase inhibitor (TKI) therapy. In both trials patients received omacetaxine 1.25 mg/m^2 subcutaneous (SC) administration twice daily (BID) for 14 days every 28 days (patients were eligible to receive up to 6 cycles of induction therapy depending on response) and omacetaxine 1.25 mg/m^2 SC administration BID for 7 days every 28 days as maintenance therapy (maintenance cycles could continue up to 24 months).

NDA 22374 was presented at the Oncologic Drugs Advisory Committee (ODAC) on March 22, 2010. The ODAC discussion focused on the lack of a companion diagnostic to identify the trial population/intended patient population with the Bcr-Abl T315I mutation (for the trial and after approval). The question posed to ODAC was: "*Should a well characterized in vitro diagnostic to identify patients with the T315I mutation be*

required and reviewed by the FDA and correlated to clinical trial results prior to approval of omacetaxine for the proposed indication?"

The committee vote was 7 "*Yes*" to 1 "No".

The following is a summary of the ODAC findings for NDA 22374:

- The Indication proposed for Omapro depends on a companion diagnostic test for T315I mutation.
- Significant clinical impact is likely from any false results (especially false positives).
- Reliable test performance (matching the clinical trial) is needed to assure patients similar to those in the trial are identified post-approval.
- A variety of non-standardized, non-reviewed assays was used to accrue patients for the trial. Reliable test performance is not assured by the trial.
- The appropriate "positive" cut-point is unknown.
- Reliable selection of patients for post-approval treatment with Omapro is not yet assured.

Thus, NDA 22347 received a Complete Response letter in April of 2010 on the basis that the intended patient population was not able to be adequately identified given the lack of a reliable test for the determination of the gene mutation status; two different *in vitro* tests were used in the pivotal trial the comparability of which tests was unknown; and the lack of T315I mutational status confirmation by central laboratories in almost half (23 of the 66) of the patients (including 5 of 11 responders). NDA 22347 was subsequently withdrawn in February of 2011.

A pre-NDA meeting was held on June 30, 2010 to discuss a path forward for the trials discussed at ODAC. At this meeting an agreement was reached that "A combined data set of a homogeneous patient population with respect to prior therapy from trials CML-202 and CML-203 could be the basis of a New Drug Application (NDA) in a third-line setting". The homogeneous patient population were patients with CML (chronic, accelerated, or blast phase) who have failed imatinib (as in trial CGX-635-CML-202 or CML-202) or who failed or have intolerance to two or more TKI therapies (as in trial CGX-635-CML-203 or CML-203).

On March 30, 2012, Cephalon, Inc. (a subsidiary of Teva) submitted NDA 203585 with the supporting data based on results of analyses of a subset of patients with intolerance to or refractoriness to 2 prior TKI from two phase II trials (CML 202 and CML 203) in CML (referred to as analysis CGX-635-CML 300 or Analysis CML-300) as discussed in the pre-NDA meeting.

The proposed indication submitted was *"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."*

The Application was filed as a standard review designation. On July 18, 2012, the Applicant submitted a request for dispute resolution regarding the standard review designation. In this submission, the Applicant clarified that their proposed indication is for a 3rd line indication (after treatment with 2 prior TKIs). On August 03, 2012, the Office of Hematology Oncology Products granted Teva's Dispute Resolution Appeal, designating the application as PRIORITY review.

2.6 Other Relevant Background Information

A search of the literature and query of the EMA did not find approval of omacetaxine in other countries/regions.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the eCTD submission was adequate and sufficient to allow substantive review.

3.2 Compliance with Good Clinical Practices

The applicant states that the trial was conducted in accordance with the ethical principles originating from the Declaration of Helsinki as amended in Tokyo, Venice, Hong Kong and South Africa, and Good Clinical Practices (GCP), and in compliance with local regulatory requirements and 21 CFR 312. No new trial was conducted for the supporting data for NDA 203585. Per the clinical review of the previously submitted NDA 22374, each participating center submitted the protocol and patient information and consent forms to their Independent Ethics Committee (IEC), or to their Institutional Review Board (IRB). The IEC/IRB written unconditional approval was obtained and submitted to the sponsor before the start of the trial. The IEC/IRB was informed of all subsequent protocol amendments. Changes in the trial were not implemented without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to the patients. In these cases the IEC/IRB was notified within 5 days of the change. The IEC/IRB was also informed of unanticipated problems or unexpected serious adverse experiences that occurred during the trial that were likely to affect the safety of the patients, or the conduct of the trial. Also, written reports were provided to the IEC/IRB annually or more frequently if requested on any changes significantly affecting the conduct of the trial and/or increasing risk to the patients.

However, based on prior inspection of clinical sites (during review of NDA 22347), OSI has determined that data from sites 22 and 30 are not reliable and are not to be used in the Agency's analyses of safety and efficacy. Per the August 04, 2010 EMA Inspection Report Tekinex Prof. Hochhaus (inv. site 030), "…important data concerning efficacy (hematologic response) and safety (hematotoxicity) were not collected from the sites. Thus, these relevant data were not provided to the Data Monitoring Committee (DMC), which evaluated the hematologic response (primary efficacy criterion), nor were they taken into account for the evaluation of safety, especially with regard to hematotoxicity. Thus these instructions are not considered adequate. This relevant issue was also discussed with the sponsor. Furthermore, the instructions in section 8.6 of the clinical trial protocol: The principal investigator should continue to report any significant follow-up information to the sponsor up to the point the event has resolved" are not precise enough to ensure complete collection of efficacy and safety data, especially in relation to the primary efficacy endpoint. Results of unscheduled laboratory tests were only in a few cases entered in the CRF and reported. Several laboratory results which were considered significant and AE related (fulfilling the clinical trial protocol criteria) were not entered in the CRF by the site."

Per the September 13, 2010 EMA Integrated Inspection Report EMEA/INS/GCP/2010/07, Tekinex, km , "The instructions for collection of unscheduled laboratory data and for relevant AE follow up information were inadequate (see also description in section 3.4.1). It was not ensured that all necessary data about the disease course and patients conditions was reported from the site. This is of special importance because the assessment of the hematologic response (primary efficacy) and the safety analysis were based on these data. This observation led to one critical and two major findings. "Major" findings, as per the August 12, 2010 Premier Research Group Final Inspection Report, carry the consequence of rejection of the data. Additionally, at both investigator sites not all completed CRF pages with results of unscheduled laboratory tests were collected by the monitors." "Discrepancies between medical files and IPDL related to adverse events have been noted during the inspection..." "At both inspected sites, source data verification revealed several discrepancies between source data and individual patient data listings (IPDL), CSR respectively, which were graded as major findings."

3.3 Financial Disclosures

Disclosure of financial interests of the investigators who conducted the clinical trials supporting his NDA was submitted in the FDA form 3454. FDA Form 3455 has been included in this submission for (b) (6). Details of (b) (6) disclosable financial arrangements and interests are provided below, along with a description of steps taken to minimize the potential bias of clinical trial results by any of the disclosed arrangements or interests.

The Sponsor discloses that significant payments made on or after February 2, 1999, from the sponsor of the covered trial, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria have been received by the following investigators:

- (b) (6)
  - (b) (4) (Study CGX-635-CML-202) and (b) (4) (CGX-635-CML-203)
- (b) (6)
  - (b) (4) (Study CGX-635-CML-202) and (b) (4) (CGX-635-CML-203)

Reported payments (b) (6) are honoraria in the amount of $800.00, meeting attendance funds in the amount of $2,500.00, and consulting fees in the amount of $24,000.00 for a total of $27,300.00, per the applicant's report.

Reported payments (b) (6) (paid by Cephalon from January 2006 through September 2011) are honoraria in the amount of $408,050.00 and travel expenses in the amount of $8,604.42 for a total of $416,654.42, per the applicant's report.

Potential bias of clinical trial results by the above mentioned investigators were minimized by the following steps:

- The site was 1 of 28 sites from 10 different countries that participated in the CGX-635-CML-202 trial and the site was 1 of 25 sites from 9 different countries that participated in the CGX-635-CML-203 trial (b) (6) enrolled 13 of the 103 patients in the CGX-635-CML-202 trial. (b) (6) enrolled 24 of 100 patients in the CGX-635-CML-203 trial.
- The site was 1 of 28 sites from 10 different countries that participated in the CGX-635-CML-202 trial and the site was 1 of 25 sites from 9 different countries that participated in the CGX-635-CML-203 trial (b) (6) enrolled 2 of the 103 patients in the CGX-635-CML-202 trial. (b) (6) enrolled 3 of the 100 patients in the CGX-635-CML-203 trial.
- An Independent Data Monitoring Committee analyzed the efficacy results of the trials.
- ChemGenex, a wholly-owned subsidiary of Cephalon, audited the sites to ensure GCP compliance and data integrity.

Removal of patients from the analysis that were enrolled by (b) (6) do not significantly affect the trial results. The financial disclosures do not appear to affect the results that support the efficacy of omacetaxine in the proposed indication.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to CMC review. Per the CMC review, The NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product and from the CMC perspective, this NDA is recommended for approval.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Please refer to Pharmacology/Toxicology review. No carcinogenicity studies have been conducted with omacetaxine. Omacetaxine was genotoxic in an *in vitro* chromosomal aberration test system in Chinese hamster ovary (CHO) cells. Omacetaxine was not mutagenic when tested in an *in vitro* bacterial cell assay (Ames test), nor did it induce genetic damage using an *in vivo* mouse micronucleus assay.
Omacetaxine may impair male fertility. Studies in mice demonstrated adverse effects on male reproductive organs. Bilateral degeneration of the seminiferous tubular epithelium in testes and hypospermia/aspermia in the epididymides were reported at the highest dose group of 2.33-1.67 mg/kg/day (7 to 5 mg/m^2/day) following subcutaneous injection of omacetaxine for six cycles over six months. The doses used in the mice were approximately two to three times the clinical dose (2.5 mg/m^2/day) based on body surface area.

Per the Pharmacology/Toxicology review, the recommendation is approval of omacetaxine from the pharmacology and toxicology standpoint for the proposed indication.

4.4 Clinical Pharmacology

Please refer to Clinical Pharmacology review. Per the Clinical Pharmacology review, the submission is acceptable from a Clinical Pharmacology perspective.

4.4.1 Mechanism of Action

The mechanism of action of omacetaxine is reversible inhibition of protein elongation, which selectively impacts short-lived proteins.

4.4.2 Pharmacodynamics

Please refer to Clinical Pharmacology review. No PD studies were conducted for this submission.

4.4.3 Pharmacokinetics

Please refer to Clinical Pharmacology review. The absolute bioavailability of omacetaxine has not been determined. Omacetaxine is rapidly absorbed following subcutaneous administration, and maximum concentrations are achieved in 0.5 to 1 hourThe steady-state (mean ± SD) volume of distribution of omacetaxine is approximately 141 ± 93.4 L following subcutaneous administration of 1.25 mg/m^2 twice daily for 11 days. The plasma protein binding of omacetaxine is less than or equal to 50%. Omacetaxine is primarily hydrolyzed to 4′-DMHHT via plasma esterases with little hepatic microsomal oxidative and/or esterase-mediated metabolism *in vitro*. The major elimination route of omacetaxine is unknown. The mean percentage of omacetaxine excreted unchanged in the urine is less than 15%. The mean half-life of omacetaxine following subcutaneous administration is approximately 6 hours.

A PMR has been requested to address optimal dosing, as BSA based dosing has been deemed as suboptimal for adequate exposure in those with lower BSAs and efficacy PK trial exploring fixed dosing has been requested.

A PMR has been requested to further characterize the pharmacokinetics (absorption, distribution, metabolism, and excretion) of omacetaxine mepesuccinate and metabolites.

4.5 Division of Medication Error Prevention and Analysis

The applicant initially proposed that omacetaxine (b) (4) [redacted] Review of the studies/analyses by DMEPA, DRISK, Microbiology, Pharmacology/Toxicology, Safety, and Clinical Review teams found that (summarized from the June 25, 2012 Correspondence from the Agency to the applicant), although the pharmacology of omacetaxine is not completely understood, it inhibits protein synthesis and has been found to have genotoxic potential (using measure of chromosome aberrations), and to cause embryolethality in mice. The

primary toxicity in animals was found to be bone marrow depletion and thrombocytopenia with serious/non-reversible hemorrhage and cardiac toxicities. Additionally, the "environmental" risks (b) (4) are not well-defined, leading to unresolved safety (b) (4)) (4) (b) (4) The applicant's proposed disposal process for the drug was also deemed inadequate and did not address the safe handling and disposal of the waste chemotherapy drug product and the associated materials used during preparation, reconstitution, and injection. The proposed disposal process did not address the concern of storing the waste product until the container is ready to be shipped back to the processing center and did not fully address the details of handling and disposal of the sharps container. It is unclear from the submission whether in case of a vial breakage, the drug can be leached into the container and leached to the outside or whether the proposed container approved to contain all the waste products used in the process of using this drug (i.e., chemotherapy related as well as sharps).

The Agency determined that additional information was needed to be submitted by the applicant regarding accidental exposure of omacetaxine (b) (4) and an analysis of the likelihood of the scenario occurring and the severity/sequelae of these various exposure scenarios.

(b) (4)

(b) (4)

Reviewer Comment: (b) (4)

The agency proposes (b) (4) *the drug be prepared and administered in the clinical setting by a health care professional. This recommendation intends to decrease environmental exposure to this genotoxic chemotherapeutic drug* (b) (4)

Also, the initially proposed trade name Omasona was not approved (see June 18, 2012 OSE Proprietary Name Review).

The following is extracted from the OSE review:

(b) (4)

(b) (4)

The applicant has proposed the new trade name Synribo, which is currently under review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 below summarizes the clinical trials from which the post-hoc patient population for Analysis CML-300 was selected (by applicant with prior agreement from the Agency) in support of the proposed indication.

Table 3 Clinical Trials

Trial ID	Design	Regimen	# Subjects
CGX-635-CML-202 (CML-202)	Phase 2, open-label, multicenter	Induction: Subcutaneous omacetaxine 1.25 mg/m² twice daily for 14 consecutive days every 28 ±3 days Maintenance: 1.25 mg/m^2 twice daily for 7 days every 28 ±3 days	103
CGX-635-CML-203 (CML-203)	Phase 2, open-label, multicenter	Induction: Subcutaneous omacetaxine 1.25 mg/m² twice daily for 14 consecutive days every 28 ±3 days Maintenance: Subcutaneous omacetaxine 1.25 mg/m^2 twice daily for 7 days every 28 ±3 days	100
CGX-4.2/4.3 (CML-4.2/4.3)	Phase 2, open-label multicenter, single-arm/(4.3 was an extension to 4.2)	Induction (CML-4.2): omacetaxine administered at 1.25 mg/m^2, subcutaneous, twice daily for 10-14 consecutive days of every 28–45 days of 1-2 cycles Maintenance (CML-4.3): omacetaxine administered at 1.25 mg/m^2 subcutaneous, twice daily for up to 7 consecutive days of every 28 days	4

Reviewer comment: *The efficacy and safety populations were selected from these trials, as described above, based on Agency and applicant agreement to evaluate a subpopulation of patients with intolerance/resistance to 2 or more prior TKIs with one TKI being imatinib. This population excludes patients with CML-BP. As such, the Analysis CML-300 population (from CML-202 and CML-203) for efficacy and CML-SC (subcutaneous) population (from CML-202, CML-203, and the 4 subjects in trial CML-4.2/4.3) for safety, are adequate to support review of the NDA for the indication of omacetaxine in the adult patient population with CML-CP and CML-AP as third line therapy.*

5.2 Review Strategy

Review was conducted of applicant's eCTD submission of background, trial protocol, analyses, and data, and current literature pertaining to CML and available treatments. The goal was to evaluate the level of evidence provided to support approval of the new drug omacetaxine as third line therapy for CML-CP and CML-AP in adult patients who were intolerant to or resistant to treatment to two or more TKIs, and the associated labeling claims. The analyses were conducted on the subset of patients from trials CML-202 and CML-203 (for efficacy) and CML-4.2/4.3 for safety) meeting the criteria of having received 2 or more approved TKIs previously and at a minimum, having evidence of resistance or intolerance to dasatinib and/or nilotinib. The raw and derived datasets submitted were analyzed using JMP.

5.3 Discussion of Individual Studies/Clinical Trials

The applicant submitted an analysis (Analysis CML-300) on a subset of patients with CML-CP and CML-AP who had not responded to imatinib (as in trial CML-202) and were resistant to or intolerant to 2 prior TKIs (as in trial CML-203) including dasatinib and nilotinib from previously conducted phase 2 non-randomized, open label, multicenter trials in adults with CML-CP, CML-AP, and CML-BP. The subset of patients from trials CML-202 and CML-203 (excepting a total of 44 patients with CML-BP) including 81 patients with CML-CP and 41 patients with CML-AP form the basis of the applicants efficacy evaluable patient population. These patients, excluding an additional 3 patients from sites 22 and 30 due to data unreliability, consisting of a final total of 78 patients with CML-CP and 41 patients with CML-AP form the basis of the Agency's efficacy evaluable patient population. The safety evaluable population determined by the applicant consists of all subjects patients with CML-CP and CML-AP who received at least one dose of omacetaxine in trials CML-202, CML-203, and CML-4.2/4.3 for a total of 108 patients with CML-CP and 55 patients with CML-AP, while the safety evaluable population determined by the Agency consists of the same population excepting 5 patients from sites 22 and 30 due to data unreliability for a total of 103 patients with CML-CP and 55 patients with CML-AP. The three trials are summarized below, as follows:

Phase 2 Trials CGX-635-CML-202 and CGX-635-CML-203

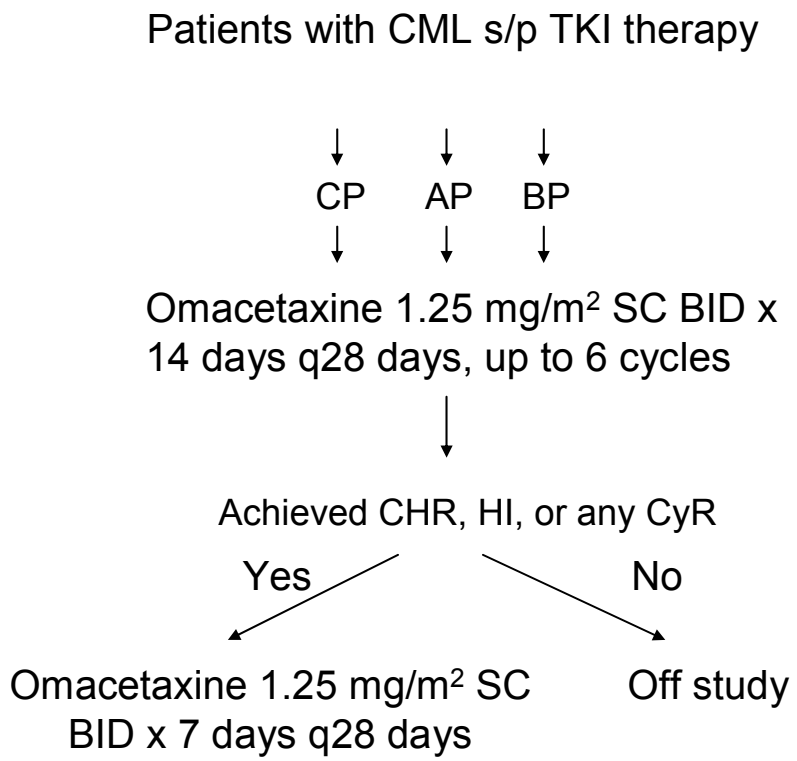
CGX-635-CML-202 (CML-202)

- Title: Phase II Open-Label Study of the Subcutaneous Administration of Omacetaxine in the Treatment of Patients with Chronic Myeloid Leukemia (CML) With the T315I Bcr-Abl Gene Mutation
- n=103

CGX-635-CML-203 (CML-203)

- Title: Phase II Open-Label Study of the Subcutaneous Administration of Omacetaxine Mepesuccinate in the Treatment of Patients With Chronic Myeloid Leukemia (CML) Who Have Failed or are Intolerant to Tyrosine Kinase Inhibitor Therapy
- n=100

Figure 1 Trial Design CML-202 and CML-203 Schematic



Trials CML-202 and CML-203 were similar in design and both were international multicenter open label single arm trials evaluating the safety and efficacy of SC omacetaxine in the treatment of adult patients with CML-CP, CML-AP, and CML-BP,

and had the safe efficacy endpoints, except for a secondary endpoint of reduction in the proportion of Bcr-Abl T315I mutation from baseline (not relevant to the current review). In both trials initial induction therapy consisted of SC omacetaxine 1.25 mg/m² BID for 14 consecutive days every 28 (± 3) days with maintenance treatment SC omacetaxine 1.25 mg/m² BID, to be administered for 7 consecutive days every 28 (± 3) days. Maintenance cycles could continue for 24 months. Depending on HR and CyR, patients could discontinue from the respective trial, transition from the induction schedule to the maintenance schedule, or if already on maintenance schedule, transition back to the induction schedule. Patients were eligible to receive up to 6 cycles of induction treatment depending on response.

Inclusion Criteria CML-202 and CML-203

- CML-202: Adults age ≥ 18 with Ph+ CML - CP, AP, or BP – with failure to prior imatinib therapy and with loss of hematologic or cytogenetic response on current or most recent therapy
- CML-203: Adults with Ph+ CML - CP, AP, or BP who received at least 2 prior TKIs, without response or with loss of hematologic or cytogenetic response on current or most recent therapy
- CML-AP
  - ≥ 15-<30% blasts in peripheral blood or bone marrow
  - ≥ 30% blasts + promyelocytes peripheral blood or bone marrow
  - ≥ 20% basophils peripheral blood or bone marrow
  - Platelet count < 100×109/L unrelated to therapy/clonal evolution
- CML-BP
  - ≥ 30% blasts in the peripheral blood or bone marrow or presence of extramedullary disease (other than spleen or liver)
- CML-CP
  - All other patients
- CML-202: Failure to prior imatinib therapy / CML-203: Failure to prior TKI therapy
  - No CHR by 12 weeks - lost or never achieved
  - No cytogenetic response by 24 weeks (100% Ph+) - lost or never achieved
  - No MCyR by 52 weeks (≥ 35% Ph+) - lost or never achieved response
  - Progressive leukocytosis
  - Progressive leukocytosis
    - Increasing WBC count on at least 2 consecutive evaluations, at least 2 weeks apart and doubling from the nadir to ≥ 20,000/μL

    or
    - Absolute increase in WBC by ≥ 50,000/μL above post-treatment nadir
- Hydroxyurea permitted immediately prior to and during the first two cycles for patients with rapidly proliferating disease
- Presence of the T315I Bcr-Abl gene mutation

  - Two central laboratories evaluated patient samples for the presence of this mutation
- Patients with lymphoid Ph+ blast crisis and candidates for BM or SCT were ineligible

- CML-203: Intolerance to TKI therapy
  - Grade 3-4 non-hematologic toxicity that does not resolve with adequate intervention
  - Grade 4 hematologic toxicity lasting more than 7 days
  - Any Grade ≥ 2 toxicity that was unacceptable to patient
- Ability to consent in writing

Exclusion Criteria CML-202 and CML-203

- New York Heart Association class III or IV heart disease, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure.
- A myocardial infarction in the previous 12 weeks.
- Another concurrent illness which would have precluded trial conduct and assessment, including but not limited to another active malignancy (excluding squamous or basal cell skin cancer and in situ cervical cancer), uncontrolled and active infection, and positive Human Immunodeficiency Virus or positive Human T-Cell Lymphotropic Virus I/II status, whether on treatment or not.
- Pregnant or lactating.
- Any medical or psychiatric condition, which may have compromised the ability to give written informed consent or to comply with the trial protocol.
- Lymphoid Ph+ blast crisis.
- Enrollment in another clinical investigation within 30 days of enrollment or was receiving another investigational agent.
- CML-202: The patient was a candidate for bone marrow or blood stem cell transplantation.

In trials CML-202 and CML-203 the study drug was self-administered by the patient outside the clinical setting.

Criteria for Dose (Cycle) Delays

CML-CP

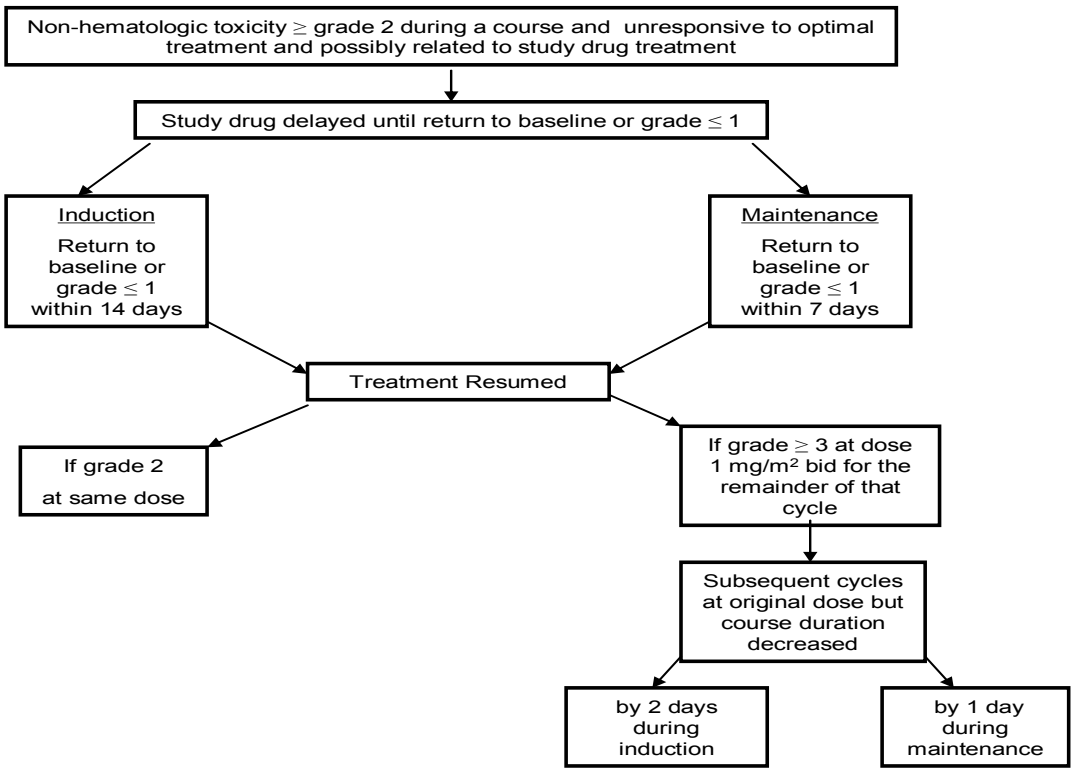
Patients who developed myelosuppression with absolute neutrophil count (ANC) $<0.5 \times 10^9$/L and platelets $<50 \times 10^9$/L had treatment delayed until reaching ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L. In subsequent treatment cycles, the dose of study drug remained the same, but the number of daily treatments was reduced by 2 days, unless the WBC $>10 \times 10^9$/L and/or absolute blast count $>5 \times 10^9$/L, in which case study drug was to be continued regardless of the neutrophil and platelet counts, giving transfusion

support if needed. Additional repeat dose reductions of 2 days were made if myelosuppression recurred or persisted after subsequent treatment cycles.

CML-AP
Patients who developed myelosuppression with absolute neutrophil count (ANC) <0.5 x 10^9/L and platelets <50 x 10^9/L had treatment delayed until reaching ANC ≥1.0 x 10^9/L and platelets ≥50 x 10^9/L. However, as a consequence of accelerated phase disease prior to the start of therapy, for patients who had neutropenia or thrombocytopenia, the dose of study drug was not modified, unless it was clear that neutropenia or thrombocytopenia were consequences of study drug toxicity and were not due to the underlying disease. In these cases, the induction treatment cycle was reduced by 2 days for the next and all subsequent treatment cycles. Additional repeat dose reductions of 2 days were made if myelosuppression recurred or persisted after subsequent treatment cycles.

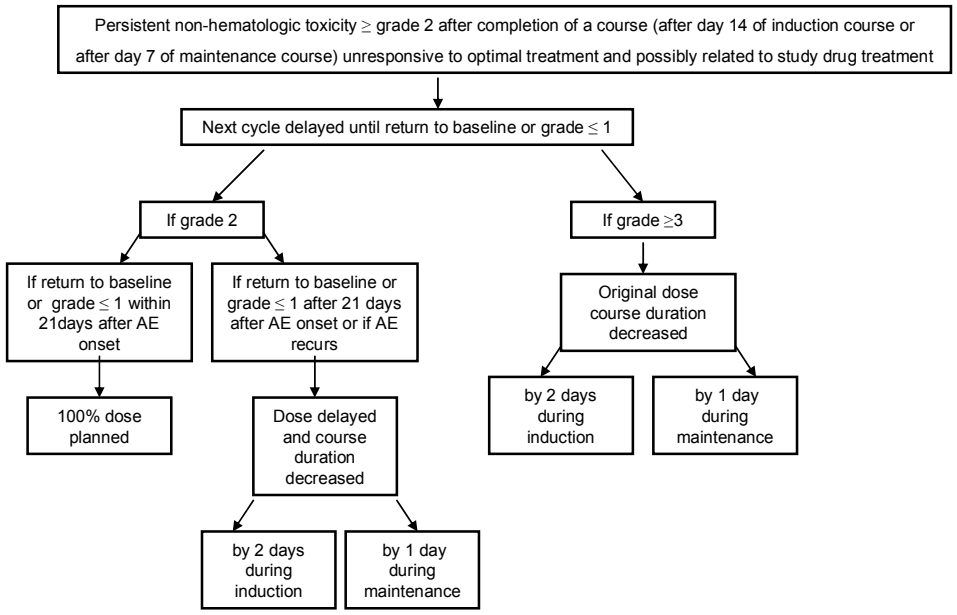
Figure 2 and Figure 3 summarize the dose delay algorithm for non-hematologic toxicities.

Figure 2 Dose Delay Algorithm for grade ≥2 Non-Hematologic Toxicities



Source: Modified from Applicant submissions: *Module 5; 5.3.5.2.4.-Protocol Study CGX-635-CML-202 Amendment 5 (May 25-2010)*–page 99 and *Protocol Study CGX-635-CML-203 Amendment 4 (May 25-2010)*–page 99.

Figure 3 Dose Delay Algorithm for Persistent Grade ≥2 Non-Hematologic Toxicities



Source: Modified from Applicant submissions: *Module 5; 5.3.5.2.4.-Protocol Study CGX-635-CML-202 Amendment 5 (May 25-2010)* –page 100 and *Protocol Study CGX-635-CML-203 Amendment 4 (May 25-2010)*–page 100.

Phase 2 Trials CGX-4.2/4.3

CGX-4.2

- Title: Phase II multicenter, single-arm, open-label study of subcutaneous homoharringtonine (HHT) alone in patients with accelerated phase chronic myeloid leukemia who are refractory to, or have relapsed on imatinib mesylate
- n=4 (all 4 included in safety analysis)

CGX-4.3

- Title: Phase II multicenter, open-label, single arm, extension trial of maintenance treatment with subcutaneous hemisynthetic homoharringtonine (HHT) as a single agent in patients with chronic myeloid leukemia (CML) who received HHT in Stragen study CGX-04.2 and achieved a complete hematological response (CHR) or returned to chronic phase
  - n=2 (2 of the 4 from CML-4.2 participated in CML-4.3; all 4 patients included in safety analysis)

Trial CML-4.2/4.3 Design

CML-4.2/4.3 was an open-label, multicenter, trial of patients with CML-AP who were refractory to, or relapsed on imatinib mesylate treatment as assessed by the loss of hematological response. In this trial, omacetaxine was administered on an outpatient setting by the principal investigator's authorized designee or by the patient themselves. During induction portion of the trial (CML-04.2) patients received 1–2 cycles of omacetaxine 1.25 mg/m^2 by SC administration BID for 10–14 consecutive days every 28–45 days. During the maintenance (extension portion of the trial) (CML-04.3) patients received 1.25 mg/m^2 by SC administration BID for up to 7 consecutive days every 28 days. Efficacy assessments were performed prior to and during omacetaxine treatment using data collected from hematologic assessments, leukemia related symptoms, physical examination (liver and spleen size, extramedullary involvement), performance assessment using Eastern Cooperative Oncology Group (ECOG) criteria, peripheral blood samples and bone marrow aspirate and/or biopsy (in the event of aspirate failure). The tolerance and toxicity of omacetaxine treatment regimen was evaluated by changes in the patient's physical examinations, vital signs, weight, liver and spleen size, and laboratory studies including routine hematology and clinical chemistry, and solicited and unsolicited adverse events (AEs). Investigators graded the toxicities using the National Cancer Institute (NCI) toxicity criteria (version 2.0). AEs were classified as hematological or non-hematological in nature. Patients were evaluated each month during trial treatment, with a final follow-up evaluation four weeks after completing all trial treatment. For both portions of the trial, safety assessments included changes in the patient's physical examinations, vital signs, weight, liver and spleen size, and laboratory studies including routine hematology and clinical chemistry. AEs were graded using the NCI toxicity criteria.

The objective of trial 04.2 was evaluation of the safety and efficacy of sc administration of omacetaxine in achieving a clinical response in patients with CML accelerated phase who were refractory to, or relapsed while receiving, imatinib treatment. Trial 04.3 was an extension of CML 04.2, and the objective of trial CML-04.3 evaluation of the safety and efficacy of sc administration of omacetaxine in patients with CML accelerated phase who either achieved a complete hematologic response or returned to chronic phase after 1 or 2 courses of omacetaxine in trial 04.2.

Inclusion Criteria CML-4.2 and CML4.3

- Adult patients age 18 to 80 years.
- CML-4.2: Patients diagnosed with Ph+ or Bcr-Abl positive CML-AP that had been confirmed by a bone marrow aspirate and/or biopsy including cytogenetics and molecular analysis that must have been completed within 28 days prior to initiation of omacetaxine.
- CML-4.3: Patients who had participated in protocol CGX-04.2
- CML-4.2: Patients must have failed to respond to, or have relapsed on imatinib.

- CML-4.3: Patient had either achieved a CHR or RCP after one or two courses of SC omacetaxine.
- The patients must have had an estimated life expectancy of at least 12 weeks.
- The patients must have had an adequate performance status as defined by a grading of 0-2 on the ECOG Performance Status Criteria.
- Female patients of child-bearing potential must have used adequate contraception (oral contraceptive pill, IUD, surgical sterilization, depot injection, contraceptive patches or barrier method in combination with a spermicide) for the duration of and at least one month after the last dose of the investigational product.
- Male patients must have been willing to use adequate contraception for the duration of and at least three months after the last dose of investigational product.
- Patients must have given written informed consent having read and understood the subject information sheet.

Exclusion Criteria CML-4.2/4.3

- CML-4.2: Patients who were planned to receive allogeneic transplantation before the end of the induction period.
- CML-4.3: Patients who did not achieve CHR or RCP of CML while treated with SC omacetaxine in protocol CGX-04.2.
- CML-4.2: Patients who had prior stem cell transplantation.
- CML-4.3: Primary resistance to omacetaxine.CML-4.2: Patients who were previously treated with combination chemotherapy or autografting for accelerated phase disease.
- CML-4.3: Reappearance of hematological features consistent with CML-AP or progression to
- CML-BP.CML-4.2: Patients who had previous blastic phase.
- CML-4.3: Ongoing grade 3-4 hematological toxicity related.
- CML-4.2: Patients who had previously been treated with omacetaxine.
- CML-4.3: Patients who needed to receive anti-leukemic agents other than omacetaxine, hydroxyurea or anagrelide during the trial.
- Female patients who were pregnant (confirmed by a serum pregnancy test) or lactating.
- For patients who had received another investigational anti-leukemic product, a washout period of two times the half-life of the product had to be observed before initiation of treatment with omacetaxine (minimum of 48 hour of wash-out). In case of grade 3–4 hematological toxicity related to any other investigational anti-leukemic product, patients did not begin treatment with omacetaxine until blood count recovery.
- Anti-leukemic agents, other than hydroxyurea or anagrelide, must have been stopped within seven days prior to the initiation of treatment with omacetaxine, and imatinib had to have been stopped at least 48 hours before starting therapy with omacetaxine. In the case of grade 3–4 hematological toxicity related to imatinib, patients were to not begin treatment with omacetaxine until blood counts recovered.

- Patients who had New York Heart Association (NYHA) class III or IV heart disease, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure.
- Patients who had creatinine levels more than 3 x upper limit of normal range (ULN) at the laboratory where the analysis was performed.
- Patients who had total serum bilirubin more than 3 x ULN in patients without clinically suspected leukemic involvement of the liver.
- Patients with aspartate aminotransferase (serum glutamic oxaloacetic transaminase) or alanine aminotransferase (serum glutamic pyruvic transaminase) more than 5 x ULN in patients without clinically suspected leukemic involvement of the liver.
- Any other reason, which the Investigator felt, would preclude safe inclusion of the patient.

Analysis CML-300

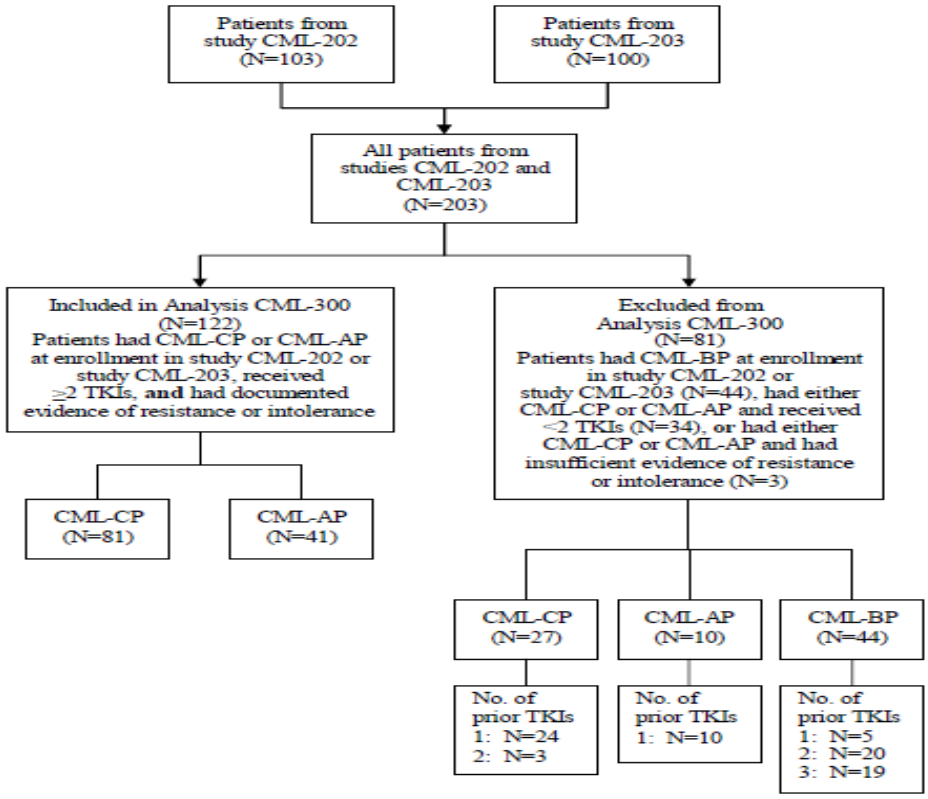
Analysis CML-300 (Efficacy population form CML-202, CML-203)

Subjects

From trials CML-202 and CML-203 a subset of adult male and female (age 18 and greater) patients who had failed prior treatment with 2 or more TKIs and at a minimum had evidence of resistance or intolerance to dasatinib nilotinib (n=122) were selected to comprised the population for Analysis CML-300 *post hoc* efficacy evaluation. The total patients from the two trials, who met the criteria of CML disease and failure to imatinib and resistance or intolerance to at least 2 prior TKIs, for inclusion in Analysis CML-300 was 122 and included 81 patients with CML-CP and 41 patients with CML-AP. See inclusion criteria for trials CML-202 and 203. For this review, the total of patients in the efficacy population will be 119 (reflecting removal of 3 patients with CML-CP from sites 22 and 30 due to data unreliability, for a total of 78 patients in the CML-CP and 41 patients in the CML-AP groups). For Analysis CML-300, patients with less than one prior TKI therapy and those with CML-BP were excluded (see exclusion criteria for trials CML-202 and CML-203).

The schematic below (Figure 4) summarizes the patient population selection for Analysis CML-300.

Figure 4 Analysis CML-300 Subject Selection Schematic



Source: Applicant submission *Module 2; 2.7.3-Summary of Clinical Efficacy*- page 9.

CML-SC (Safety population form CML-202, CML-203, CML-4.2/4.3)
The safety population (CML-SC, n=163) consists of all patients with CML-CP and CML-AP from trial CML-202, CML-203 and CML-4.2/4.3 who had had received at least one dose of subcutaneous omacetaxine and excludes a total of 44 patients with CML-BP. The total of 163 includes 108 patients with CML-CP and 55 patients with CML-AP. For this review, the total of patients in the safety population will be 158 (reflecting removal of 5 patients with CML-CP from sites 22 and 30 due to data unreliability, for a total of 103 patients in the CML-CP and 55 patients in the CML-AP groups).

Primary Objectives/Endpoints

CML-CP

- The primary objective and endpoint for patients with CML-CP was the determination of the proportion of patients who achieved major cytogenetic response at 24 weeks (MCyR: complete cytogenetic response [0% Ph+ cells] or partial cytogenetic response [> 0% to 35% Ph+])

The definition of complete cytogenetic response was 0% Ph+ cells.

The definition of partial cytogenetic response was 0% to up to 35% Ph+ cells.

CML-AP

- The primary objective and endpoint for patients with CML-AP was the determination of the proportion of patients who achieved major hematologic response at 24 weeks (MaHR: complete hematologic response or no evidence of leukemia).

The definition of complete hematologic response (CHR) was:

- Absolute neutrophil count ≥ 1.5 × 109/L
- Platelets ≥ 100 × 109/L
- No blood blasts
- Bone marrow blasts < 5%
- No extramedullary disease

The definition of no evidence of leukemia (NEL) was morphologic leukemia-free state, defined as <5% bone marrow blasts

Secondary Objectives/Endpoints were as follows:

- Evaluation of the safety and efficacy in CML- CP and CML-AP
  - Patients with CML-CP, who achieved a CHR
  - Patients with CML-AP, who returned to chronic phase (RCP)
  - Patients who achieved other hematologic responses (partial hematologic response) or hematologic improvement (HI)
  - The proportion of patients who achieved other cytogenetic (minor, minimal, none) responses
  - Time to onset of responses
  - Duration of responses (including the overall duration of MCyR)
  - Progression-free survival (PFS)
  - Overall survival
  - Evaluation of safety
    - AEs, concomitant medications, study drug exposure, clinical laboratory test results, vital signs, weight, physical examination results, ECG findings
- Evaluation of ECOG performance status

Figure 5 below, summarizes the assessment and monitoring parameters and schedules.

Figure 5 Assessments and Monitoring

Activity	Screening	Preceding each omacetaxine induction cycle[6]	Every 7 days during induction treatment (Days 7, 14, etc.)	Confirmation of response[11]	Preceding each omacetaxine maintenance cycle[12]	Maintenance cycles every 14 days[15]	Every 3 months on study[17]	Study completion, unscheduled visits, or early termination[13]
Informed consent	X							
Inclusion/Exclusion criteria	X							
Medical history	X							
Interval medical history		X[10]			X[10]			X
Physical exam	X							
Brief physical exam		X[6]			X[7]			X
Height	X							
Weight	X	X[6]			X[7]			X
Calculate body surface area	X	X			X			
Vital Signs (heart rate, blood pressure, RR, T)	X	X[9]			X[9]			X
Chest x-ray	X[1]							
ECG	X[1]	X[18]					X[18]	X[18]
Hematology[2]	X	X[6,7]	X[20]	X[11]	X[7,8]	X[15]		X
Serum Chemistry[3]	X	X[6,7]	X[20]		X[7,8]	X[15]		X
Bone Marrow Aspiration and Cytogenetics[4]	X			X[11,22]			X[17]	X[19]
BCR-ABL quantitative transcript levels by qRT-PCR[5,14]	X	X			X			X[21]
Bcr-Abl mutation analysis[14]	X						X[17]	X[21]
Urine or serum pregnancy test, HCG[8]	X							
Urinalysis	X							
Pharmacokinetic study		X[16]						
Molecular studies[14]								
Document other measures of disease and disease symptoms	X	X			X			X
Performance status	X	X[6]			X[7]			X
Drug accountability		X			X			X
Concomitant medication	X	X			X			X
Adverse event reporting		X			X			X
Omacetaxine administration		BID x 14 days			BID x 7 days			

ALT=alanine aminotransferase, BID=twice a day, CCyR=complete cytogenetic response, CyR= cytogenetic response, ECG=electrocardiogram, HCG=human chorionic growth hormone, Hct=hematocrit, Hg=hemoglobin, HHT= homoharringtonine, MCyR= major cytogenetic response, PCR=polymerase chain reaction, Ph+=Philadelphia chromosome positive, qRT-PCR=quantitative reverse transcription polymerase chain reaction, RBC=red blood cell count, RR=respiration rate, T=temperature; WBC=white blood cell count

1 May have been omitted if prior study available within preceding 1 month.
2 Complete blood counts (CBC) included Hct, Hg, RBC, WBC, differential, platelet count. Clinical and laboratory studies may have been performed and reported more often if clinically indicated.
3 Chemistry included glucose, blood urea nitrogen, creatinine, uric acid, total bilirubin, and alanine aminotransferase.
4 Bone marrow exam with cytogenetic analysis was performed by the G-banding technique. Marrow specimens were to be examined on direct short-term (24-hour) cultures; at least 20 metaphases
were to be analyzed. This may have been omitted at screening if bone marrow and cytogenetic analysis had been done in the preceding 1 month, or greater if the baseline cytogenetic analysis
performed remained an appropriate baseline measurement and the patient had not received anti-leukemic therapy during this period (other than palliative therapy e.g., Hydroxyurea)
5 Bcr-Abl quantitative transcript levels were to be obtained by quantitative polymerase chain reaction (PCR) analysis of peripheral blood in patients achieving a complete cytogenetic response
Bcr-Abl transcripts were to be detected by real-time quantitative reverse transcription-PCR (qRT-PCR) analysis on peripheral blood.
6 Weight may have been obtained on the day of or within 3 days prior to start of the treatment cycle. Results were to be reviewed prior to initiating a treatment cycle. Screening studies may have been
substituted for the initial induction treatment course if acceptable results obtained within 7 days of Cycle 1.
7 Clinical and laboratory studies may have been performed and reported more often if clinically indicated.
8 Females of child-bearing potential.
9 Vital signs (heart rate, BP, RR, temperature) were measured ≤ 30 min pre-injection of omacetaxine and 20 min post injection on day 1 of each treatment cycle. If the patient had hypotension (systolic blood pressure < 90 mm Hg), vital signs were to be taken and recorded more frequently, until the patient had stabilized. (In the case of outpatient infusions, some time points may have been omitted if logistically not poss ble, e.g., the time point occurred over the weekend.)
10 Medical History at baseline or start of study therapy was to include questioning for intercurrent symptoms experienced since Screening.
11 In patients achieving a CHR or MCyR (either complete or partial, up to 35% Ph+ metaphases) during the induction phase, the response was to be confirmed by a repeat CBC, bone marrow aspiration (for patients with a hematologic response), cytogenetics of the bone marrow aspirate (for patients with a CyR), and Bcr-Abl transcript levels by qRT-PCR of peripheral blood, at the intervals

specified below. For patient convenience, confirmatory studies could be scheduled to be done prior to the next scheduled omacetaxine treatment cycle (rather than exactly at 4 or 8 weeks, as specified below, after the initial response).
a CML-CP: Response to be confirmed ≥ 8 weeks after the initial documentation of the response, i.e., ≥ 8 weeks after the patient first met the clinical and laboratory criteria for a response.
b Accelerated and blast phase CML: Response to be confirmed ≥ 4 weeks after the initial documentation of the response, i.e., ≥ 4 weeks after the patient first met the clinical and laboratory criteria for a response.
12 On the day of, or within, 3 days prior to start of the treatment cycle. Results were to be reviewed prior to initiating a treatment cycle.
13 Additional physical examination, clinical, laboratory (e.g., hematology, chemistry) and other diagnostic studies including bone marrow aspirations, biopsies, cytogenetics and quantitative PCR studies (in patients achieving a CCyR) may have been conducted at scheduled and non-scheduled time points to evaluate safety and disease status, as clinically indicated, e.g., for a laboratory abnormality.
14 See Appendix VIII of the Protocols in the Clinical Study Reports for Studies CML-202 and CML-203 (Module 5.3.5.2).
15 To be done on Days 1 (pre-omacetaxine dose) and 14 of each maintenance treatment cycle x 3 cycles. If laboratory values demonstrated a predictable trend and it was deemed clinically acceptable, the frequency of laboratory studies could then be reduced to only on Day 1 of subsequent Maintenance treatment cycles, preceding the omacetaxine injection. If deemed clinically indicated, however, laboratory studies could be continued at a frequency of Days 1 and 14 for all or selected maintenance treatment cycles after Cycle 3.
16 In selected patients (minimum of 15 patients), plasma for HHT levels was to be obtained pre- and 30 minutes post-HHT injection on Day 1 and optionally pre- and 30 minutes post the morning (or the afternoon dose, if the patient was not available) injection of HHT on Days 7 and/or 14.
17 All patients. Additional studies may have been conducted earlier than a scheduled 3-month interval if clinically indicated, e.g., a rising level of Bcr-Abl transcript was observed.
18 ECG prior to Induction Cycles 1–3 and optionally, after completion of Day 14 of treatment, Induction Cycle 1, if the patient was available for this exam. The ECG was to be repeated at the start of maintenance therapy, if none available in prior 30 days, and then every 3 months on maintenance therapy and at study completion, unscheduled visits, or early termination. In Germany, ECGs were to be done before and after every omacetaxine treatment cycle.
19 Bone marrow aspiration/biopsy if indicated ± cytogenetics (optional).
20 Day 7 (±1), 14 (±1), and 21 (±1) studies may have been obtained at a local laboratory, with results transmitted to the study site in a timely manner as they became available.
21 May be omitted if prior study within 7 days.
22 Obtain bone marrow cytogenetic study to confirm a CyR.
Source: Applicant submission – *Module 5; 5.3.5.3.3– Study Report Body-page 39*

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The sponsor is seeking approval for omacetaxine for injection 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) including imatinib, dasatinib or nilotinib.

6.1.1 Methods

Efficacy analysis population included CML-CP and CML-AP patients from studies 202 and 203, who received ≥2 TKIs and had documented resistance or intolerance
Sample size calculation was not applicable as the data is from a post-hoc subset of patients from two fully enrolled phase 2 trials.

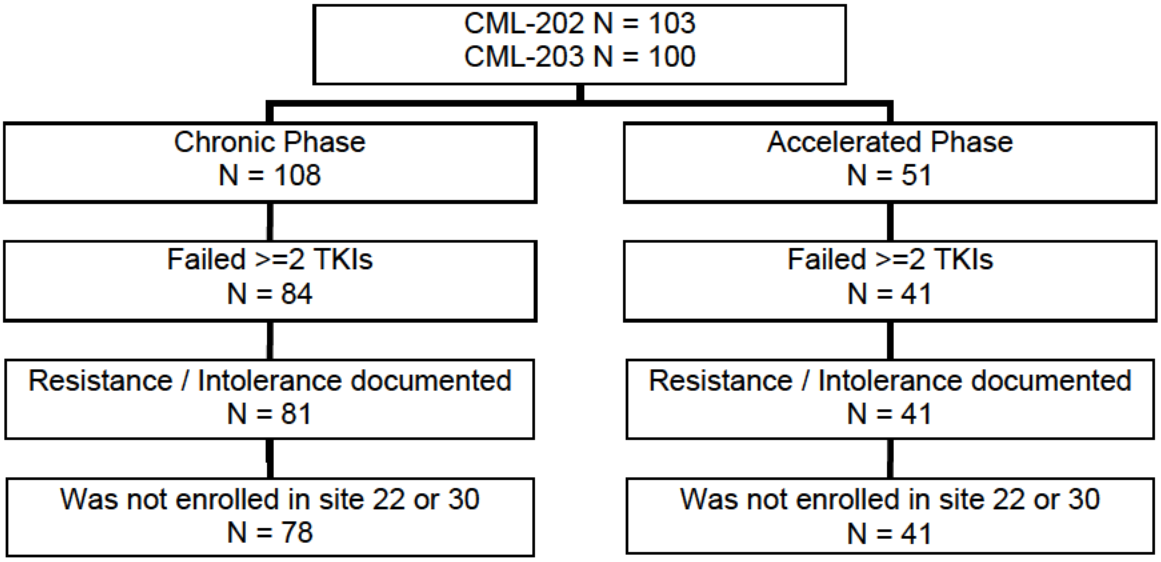
The primary endpoint was DMC adjudicated treatment response of MCyR (complete and partial cytogenetic responses) for patients with CML-CP and treatment response of

MaHR (CHR and NEL) and/or MCyR for patients with CML-AP. Analyses were performed separately by disease phase. Subgroup analysis was based on number of prior approved TKIs.

6.1.2 Demographics

A total of 122 subjects formed the efficacy population for Analysis CML-300, of which 119 were included in the Agency analyses of efficacy as discussed in this review previously and summarized in Table 4, below.

Table 4 Criteria for inclusion in FDA Efficacy Analysis



Source: FDA Statistical Review

The baseline demographic characteristics are separately evaluated for CML-CP and CML-AP groups for this efficacy analysis population. Subjects were mostly male and white. The CP and AP groups were similar in gender composition (CP 62% male and AP 61% male). Although both CP and AP consisted mostly of white subjects (CP 81% and AP 68% white), there was a much larger proportion of black patients in the AP (25%) than in the CP (5%) groups. The median age was 60 years, with median age in the CP group being 59 years and in the AP group 63 years. In total, 35% of subjects were 65 years of age or older. There were, however more subjects in the AP group who were 65 years or older (46%) compared to the CP group (29%).

The median time from CML diagnosis to first drug dose was 83 months overall (range 8,286); 73 (8,234) months for patients with CML-CP and 98 (23,286) for patients with CML-AP.

A total of 27% of patients entered the trial in baseline CHR, with 29% in the CP and 22% in the AP group entering trial in baseline CHR.

The majority of patients (54% of the total) had an ECOG score of 0 upon trial entry, with more patients having score of 0 in the CP group (67%) compared to the AP group (29%); most subjects in the AP group (54%) had a score of 1. Half (50%) of all patients had been treated with three TKIs previously. The most commonly received previous pair of TKIs by both groups was imatinib and dasatinib (CP 38% and AP 34%).

The most common non-TKI previous treatment was hydroxyurea in both groups with 51% of all Analysis CML-300 efficacy population having received prior hydroxyurea.

> Reviewer comment: Recommend that subjects who were enrolled in the trial in MCyR (CP-CML) and MaHR (AP-CML), be excluded from the efficacy analysis in order that the response at baseline not be attributed to omacetaxine, which they had not yet received. Attributing the response to omacetaxine overestimates the effect of the drug.

The demographics of the efficacy population for Analysis CML-300 are summarized in Table 5, below.

Table 5 Efficacy Population Baseline Characteristics

	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

Source: FDA Statistical Review

Table 6 Efficacy Analysis Subject Disposition

	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)

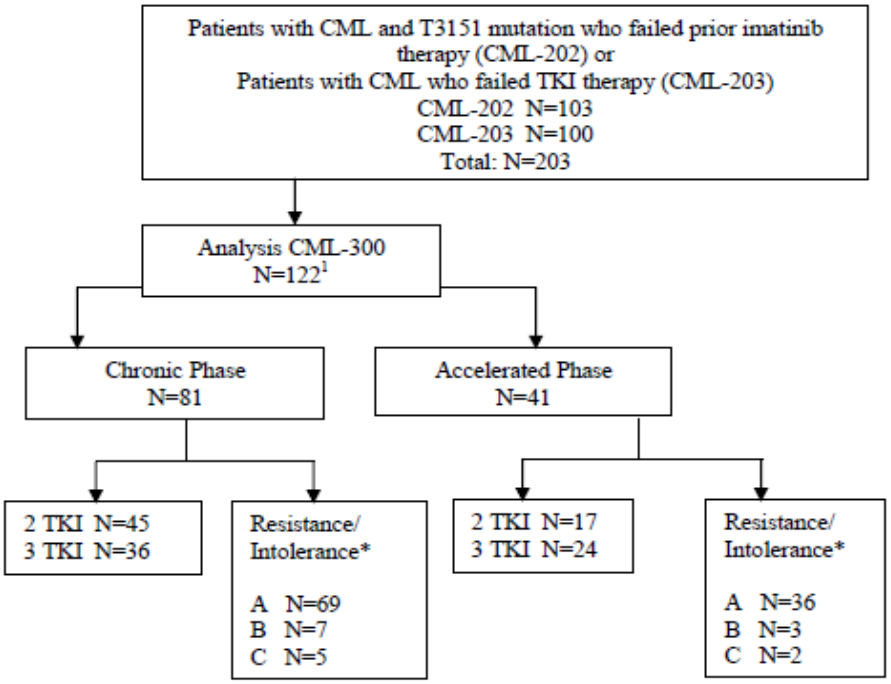
Source: FDA Statistical Review

6.1.3 Subject Disposition

Of the 203 patients in trials CML-202 and CML-203, 44 patients with blast phase CML, 24 patients with CML-CP who had failed only 1 TKI; 3 patients with CML-CP whose resistance or intolerance was not documented, and 10 patients with CML-AP whose resistance or intolerance was not documented were excluded from Analysis CML-300. Figure 6 below summarizes patient disposition and selection for Analysis CML-300 efficacy population.

Of the 122 subjects meeting criteria for selection for Analysis CML-300 (CML-CP n=81; CML-AP n=41) three patients (with CML-CP) were not included in Agency efficacy evaluation due to deficiencies found during inspection (NDA 22374) in sites 22 and 30.

Figure 6 Subject Disposition



*Resistance/intolerance categories: A=Resistance to ≥ 2 TKIs; B=Intolerance to ≥ 2 TKIs; C=Intolerance to 1 TKI and resistance to another .

Source: Applicant submission *Module 5; 5.3.5.3.3.-Study Report Body*- page 54

6.1.4 Analysis of Primary Endpoint(s)

Sample size was not based on statistical considerations and subgroup analysis was by number of prior TKI therapies. Per statistics review team, determination of sample size calculation was not applicable as the efficacy population was derived from two fully enrolled phase 2 trials. Subgroup analysis is relevant for and based on number of prior approved TKI therapies.

The primary efficacy endpoints are major cytogenetic response (MCyR; complete and partial cytogenetic response) for patients with CP-CML in the CML-300 analysis and major hematologic response (MaHR; complete hematologic response and no evidence of leukemia) and/or MCyR for patients with CML-AP in the CML-300 analysis. The definition of complete cytogenetic response was 0% Ph+ cells. The definition of partial cytogenetic response was 0% to up to 35% Ph+ cells. The definition of complete hematologic response (CHR) was: Absolute neutrophil count ≥ 1.5×10^9/L; Platelets ≥ 100×10^9/L; No blood blasts; Bone marrow blasts < 5%; No extramedullary disease. The definition of no evidence of leukemia (NEL) was morphologic leukemia-free state, defined as <5% bone marrow blasts.

> **Reviewer comment:** The endpoints were acceptable as clinically relevant and have been previously used for regulatory action in TKI approvals.

Per the applicant's analysis (n=122), MCyR rate in CML-CP was 19.8% (16/81) with median duration of 17.7 months (3.1 months mean time to onset),and lower in patients who received 3 prior approved TKIs (11.1%) compared to those who received 2 prior approved TKIs (26.7%). MCyR rate was 18.8% in patients with resistance to 2 or more TKIs (the number was too small to allow conclusions about response rate in those who were intolerant to 2 or more TKIs, or in those with intolerance to 1 TKI and resistance to another. Per the applicant's analysis (n=122), MaHR rate in CML-AP was 26.8% (11/41) with median duration of 9.0 months (1.1 month mean time to onset), and lower in those who had received 3 prior approved TKIs (20.8%) compared to those who had received 2 prior approved TKIs (35.5%). There was no MCyR achieved/reported in any patients with CML-AP in this analysis. The MaHR rate in patients with resistance to 2 or more TKIs was 27.8% (the number was too small to allow conclusions about response rate in those who were intolerant to 2 or more TKIs, or in those with intolerance to 1 TKI and resistance to another).

Agency (FDA) statistical analysis, including Analysis CML-300 efficacy population (n=119) who had best response documented at trial entry, found 20.5% MCyR response rate in CML-CP with mean and median time to response of 3.1 and 2.6 months, respectively, and duration of response of 17.7 months, and 26.8% response rate in CML-AP with mean and median time to response of 1.1 and 0 months, respectively, and duration of response of 9.0 months.

Agency (FDA) statistical analysis, excluding Analysis CML-300 patients with best response at trial entry (2 from CML-CP group and 6 from CML-AP group- these patients were deemed in baseline best response by the DMC.) found 18.4% MCyR response rate in CML-CP (16/76) with mean and median time to response of 3.5 and 2.8 months, respectively, and duration of response of 12.5 months, and 14.3% response rate in CML-AP (5/35) with mean and median time to response of 2.3 and 2.5 months, respectively, and duration of response of 4.7 months. Table 7 below, summarizes the primary endpoint efficacy analysis results.

Table 7 Primary Efficacy Analysis

	Chronic (MCyR)	Accelerated (MaHR)
Number (%) of responders	16 (20.5%)	11 (26.8%)
Time to Onset of Response (months)[1]		
Mean, Median	3.1, 2.6	1.1, **0.0**
Min, Max	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 presented with "best cytogenetic response at study entry"
[#] Six responders presented with "best hematologic response at study entry"

Source: FDA Statistical Review.

Reviewer comment: Patients with best response at trial entry should not be evaluable for treatment-induced response. The response rates should be based on evaluation of data from those patients who did not have best response at trial entry.

Table 8 Response by Disease Phase

	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	-

Source: FDA Statistical Review

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary efficacy endpoints for Analysis CML-300 included progression free survival (PFS) and overall survival (OS), summarized in the Table 9 and Table 10 below. The median time to progression was 9.7 months for patients with CML-CP, and 4.7 months for patients with CML-AP. The median overall survival was 33.9 months for patients with CML-CP, and 16.2 months for patients with CML-AP.

Table 9 Progression Free Survival

	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

Source: FDA Statistical Review

Table 10 Overall Survival

	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

Source: FDA Statistical Review

Reviewer Comment: PFS and OS are not evaluable from single-arm trials because of the lack of a comparator arm. The data is provided for completeness, but will not be relied upon for labeling purposes.

6.1.6 Other Endpoints

Not applicable for this review.

6.1.7 Subpopulations

Subgroup analysis by age, gender, and race are as follows:

- Age
  - 29% CP, 46% AP ≥65 years of age
  - Higher MCyR rate in <65 vs. ≥65 years (26% vs. 9%) in CP
  - Higher MaHR rate in ≥65 vs. <65 years (42% vs. 14%) in AP

- Gender
  - 38% CP, 39% AP were female
  - Higher MCyR rate in men vs. women (23% vs. 17%) in CP
  - Higher MaHR rate in men vs. women (32% vs. 19%) in AP

- Race
  - 81% CP, 68% AP were Caucasian
  - Similar MCyR rate in Caucasian & non-Caucasian (21% vs. 20%) in CP
  - Higher MaHR rate in Caucasian vs. non-Caucasian (29% vs. 23%) in AP

Patients with CML-CP who were younger than 65 years of age had a higher response rate compared to the older patients. Patients with CML-AP younger than 65 years of age had a lower hematologic response rate compared to those who were 65 years or older. In both CML-CP and CML-AP groups, men had a higher response rate compared to women. Response rates were similar for whites and non-whites.

Table 11 Response by Demographics

	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

Source: FDA Statistical Review

> Reviewer comment: These subgroup analyses are at best exploratory as numbers are too small to allow for a definitive conclusion regarding the effect of these parameters on efficacy. However, there is a suggestion that efficacy discrepancy associated with may be related to lower exposure in females based on lower body surface area (BSA). AUC in women was found to be approximately 64% of AUC in men. See clinical pharmacology review. The applicant should conduct efficacy PK trials to explore optimal dosing regimen with fixed dosing.

The primary endpoint result by number of prior approved TKIs received was higher in patients with CML-CP and in patients with CML-AP who had been treated previously by two TKIs (i.e. those for whom omacetaxine administration constituted third-line therapy). Most patients were resistant to ≥ 2 TKIs, and for the few that were not in this category, the response analysis by resistance/intolerance status was not informative, as the numbers were too small to allow for a meaningful conclusion regarding the role of this parameter on efficacy. The response rates by resistance/intolerance and line of therapy are summarized in Table 12, below.

Table 12 Subgroup Analysis by Resistance/Intolerance Status and Number of Prior TKIs Received

	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
Source: FDA Statistical Review

Reviewer Comments: MCyR rate appears to be higher in those patients who have received less prior therapy (as expected). Patients who were resistant to prior TKIs appear to have less responsive disease than those who were intolerant (as expected).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosing recommendation is adequate and appropriate for the proposed subcutaneous route of administration. However, per clinical pharmacology analysis it appears that lower body surface area may result in less drug exposure and explain the lower response rates in subjects with lower BSA. It is recommended that efficacy PK trial/s be conducted for evaluation of whether fixed dosing or BSA-based dosing is more optimal. See Clinical Pharmacology Review. Also, the volume of the injectable solution will be lower than that of the clinical trial formulation (to obtain the same dose) as per the recommendations of the Agency in the 2010 CR for NDA 22374. However, this change is unlikely to affect bioavailability, safety, or efficacy of subcutaneously administered omacetaxine.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The median time to response among responders was reported to be 2.6 months and 0 months for the chronic phase and accelerated phase patients respectively. The estimated median duration of response was 17.7 months for patients with CML-CP and 9.0 months for patients with CML-AP.

The time to onset and duration of response calculations included 2 patients with CML-CP and 6 patients with CML-AP who had a best response at trial entry (discussed previously in this review), summarized in Table 14**Error! Reference source not found.**.

Table 13 Time to and Duration of Response CML-300

	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
Source: FDA Statistical Review

FDA Analysis of the data after removal of the 8 patients with best response at trial entry found the following results, summarized in Table 14.

Table 14 Clinical Response Excluding Patients with Best Response at Trial 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
Source: FDA Statistical Analysis

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy or analysis issues from the clinical perspective. See Statistical Review.

7 Review of Safety

Safety Summary

7.1 Methods

The safety analysis was conducted using the safety population data (103 subjects in the with CML-CP and 55 subjects with CML-AP, comprising a selected set of patients who received at least one dose of SC omacetaxine as described in more detail in previous sections (sections 5 and 6, and elsewhere) in this review. The analyses were conducted using raw datasets in the JMP program. The Applicant's major safety analyses were reproduced. The major discrepancies between the Applicant and Agency analyses were regarding the use of investigator attribution to determine whether an event was related to study drug. The Agency does not support the use of investigator attribution in single-arm trials.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The data from patients with CML-CP and CML-AP in trials CML-202, CML-203, and CML-04.2/04.3 were used. These trials, described in sections 5 and 6 of this review, evaluated administration of subcutaneous omacetaxine in patients with CML.

7.1.2 Categorization of Adverse Events

Adverse Events (AEs) were documented throughout the course of the primary studies, CML-202 and CML-203. All patients with previously reported or new AEs were followed until resolution of the AE or when the AE was "no longer clinically significant". Patients withdrawn from the studies with an ongoing AE were followed clinically until the adverse event was completely resolved, stable or permanent. All AEs were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) version 10.0. Adverse events were coded relative to the system organ class (SOC) and preferred term. All AEs were graded according to NCI CTCAE v 3.0 criteria in CML-202 and CML-203. In this review, the preferred terms for the adverse events of asthenia and fatigue were combined into "asthenia/fatigue".

Trial 04.2/04.3 enrolled a total of 4 patients. AEs and use of concomitant meds were documented in a similar fashion to CML-202 and CML-203. However, only Serious Adverse Events (SAEs) were monitored until they were resolved, considered stable or attributed to the patient's stable or chronic condition or intercurrent illness(es). AEs were categorized using MedDRA and graded per NCI CTCAE v 2.0 in trial CML-04.2/04.3.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The data from the studies using the SC route of administration of omacetaxine are presented and pooled, as summarized in Table 15, below. These analyses were deemed appropriate for pooling because they evaluated populations that had the same disease and received the same dose/schedule of omacetaxine.

Table 15 Clinical Trials Sources of Data for FDA Safety Population (CML-SC) Analysis

Clinical Trial	Applicant Analysis CML-CP	Applicant Analysis CML-AP	FDA Analysis CML-CP	FDA Analysis CML-AP
CML-202	62	20	57	20
CML-203	46	31	46	31
CML-04.2/04.3	0	4	0	4
Total	108	55	**103***	**55**

* Removal of the 3 patients from sites 22 (France) and the 2 patients from site 30 (Germany) due to major inspection findings invalidating the data

All 5 patients (3 patients from sites 22 in France and the 2 patients from site 30 in Germany) excluded from the FDA safety analysis due to major inspection findings invalidating the data were from CML-202, CML-CP group.

7.2 Adequacy of Safety Assessments

The safety assessments and monitoring were adequate. Table 16 summarizes assessments and monitoring for trials CMl-202 and CML-203.

Table 16 Safety Assessment Schedule

Activity	Screening	Preceding each induction cycle	Every 7 days during induction treatment (Days 7, 14, etc.)	Preceding each maintenance cycle	Maintenance Cycles Every 14 days	Study Completion, Unscheduled Visits, or Early Termination
Baseline Demographics	X					
Physical exam	X					
Brief physical exam		X		X		X
Weight	X	X		X		X
Vital signs (HR, BP, RR,T)	X	X		X		X
ECOG performance status	X	X		X		X
Hematology	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X
Concomitant medication	X	X		X		X
Adverse event reporting		X		X		X
Dosing		BID x 14 days		BID x 7 days		

HR=heart rate, BP=blood pressure, RR=respiratory rate, T=temperature

Source: Applicant submission *Module 5; 5.3.5.3.28 Integrated Analysis of Safety* – page 1238.

Reviewer comment: The assessment and monitoring parameters and schedule were adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Safety Population Demographics

The baseline demographic characteristics are separately evaluated for CML-CP and CML-AP groups for this safety analysis population. Subjects were mostly male and white. The CP and AP groups were similar in gender composition (CP 64% male and AP 62% male). Although both CP and AP consisted mostly of white subjects (CP 72% and AP 57%), there was a much larger proportion of black patients in the AP (20%) than in the CP (6%) groups. The median age was 58 years, with median age in the CP group being 58 years and in the AP group 56 years. In total, 30% of subjects (47/158) were 65 years of age or older. There were, less subjects in the CP group who were 65 years or older (26% [27/103]) compared to the AP group (36% [20/55]).
The median time from CML diagnosis to first drug dose was 73 months overall (range 7.9, 285.6); 61.5 (7.9, 234) months for patients with CML-CP and 91.4 (20.3,285.6) for patients with CML-AP.

Half of patients (50% of the total) had an ECOG score of 0 upon trial entry, with more patients having score of 0 in the CP group (62%) compared to the AP group (25%); most subjects in the AP group (59%) had a score of 1.

Table 17 Safety Population (CML-SC) Demographics

	CML-CP n=103	CML-AP n=55	Total n=158
Age (years)			
Median (range)	58 (20,83)	56 (23,83)	58 (20,83)
Gender n (%)			
Male	66 (64)	34 (62)	100 (63)
Female	37 (36)	21 (38)	58 (37)
Race n (%)			
White	74 (72)	29 (57)	103 (67)
Asian	15 (15)	9 (18)	24 (16)
Black	6 (6)	10 (20)	16 (10)
Other	5 (5)	1 (2)	6 (4)
Hispanic	3 (3)	2 (4)	5 (3)
Missing		*4 (7)*	*4 (3)*
Months since CML Diagnosis			
Median (range)	61.5 (7.9,234)	91.4 (20.3,285.6)	73.4 (7.9,285.6)
Missing		*4 (7)*	*4 (3)*
ECOG Performance Status n (%)			
0	64 (62)	13 (25)	77 (50)
1	36 (35)	30 (59)	66 (43)
2	3 (3)	7 (14)	10 (6)
3	0 (0)	1 (2)	1 (1)
Missing		*4 (7)*	*4 (3)*

Missing: Data not reported for the 4 patients from trial 04.2/04.3

The proportion of patients treated with 3 and 2 TKIs previously was similar; a total of 38% had been treated with 3 TKIs previously and a total of 39% had been treated with 2 TKIs previously. The most commonly received previous pair of TKIs by both groups was imatinib and dasatinib (CP 32% and AP 25%).

Table 18 Number of TKIs Received Previously

Number Prior TKIs n (%)	CML-CP n=103	CML-AP n=55	Total n=158
1	22 (21)	14 (25)	36 (23)
2	45 (44)	17 (31)	62 (39)
3	36 (35)	24 (44)	60 (38)

Table 19 Type of TKIs Received Previously

Prior TKI/s n (%)	CML-CP n=103	CML-AP n=55	Total n=158
Imatinib Only	22 (21)	14 (25)	36 (23)
Imatinib and Dasatinib	33 (32)	14 (25)	47 (30)
Imatinib and Nilotinib	12 (12)	3 (6)	15 (9)
Imatinib, Dasatinib, and Nilotinib	36 (35)	24 (44)	60 (38)

The same proportion of subjects in CML-CP and CML-AP had resistance to 2 or more approved TKIs (65% in each group). The number of those patients with intolerance to 2 or more approved TKIs and those patients with intolerance to 1 approved TKI and resistance to another were very small in each of the groups (CML-CP and CML-AP), as summarized in Table 20 below.

Table 20 TKI Resistance/Intolerance Status

TKI	CML-CP n=103	CML-AP n=55	Total n=158
Resistance to ≥2 Approved TKIs	67 (65)	36 (65)	103 (65)
Missing information about resistance/intolerance to TKIs	25 (24)	14 (25)	*39 (25)
Intolerance to ≥2 Approved TKIs	7 (7)	3 (5)	10 (6)
Intolerance to 1 Approved TKI and Resistance to Another	4 (4)	2 (4)	6 (4)

Study drug exposure is summarized in Table 21 below. Median drug exposure was longer (7.6 months) in patients with CML-CP compared to patients with CML-AP (1.9 months), translating to higher median dose exposure (mg/m^2) in the CML-CP group. The median number of cycles received by patients in the safety population was 5 months. Data for 39 patients is missing regarding intolerance/resistance; 36 of these 39 had received imatinib only and 3 had received two or more TKIs.

Table 21 Study Drug Exposure

	CML-CP n=103	CML-AP n=55	Total n=158
Median Exposure (months)	7.6 (0,43.3)	1.9 (0,30)	5.6 (0,43.3)
Median Number of Cycles	6 (1,41)	2 (1,29)	5 (1,41)
Median Dose Exposure During Trial (mg/m^2)	132.8 (1.2,678.1)	69.6 (1.3,814.4)	104.4 (1.2,814.4)

7.2.2 Explorations for Dose Response

No exposure/dose-response analyses were performed for either efficacy or safety due to the scarcity of the PK data. No dose-response relationships have been established, as only a single dose level of 1.25mg/m^2 was evaluated in the clinical trials under review (CML-202, CML-203, and CML-04.2/04.3).

7.2.3 Special Animal and/or In Vitro Testing

The March 26, 2010 NDA 22374 Clinical Review found (extracted from the 2010 Clinical Review): Cardiovascular toxicities, severe myelosuppression, hyperglycemia and hyperbilirubinemia were the primary clinical toxicities seen in the clinical setting. In general animal toxicology studies were predictive of the clinical toxicity profile with bone marrow being the most commonly affected organ. Other toxicities in animals included findings in the heart, GI tract, liver and the kidneys. Per the FDA Pharmacology Toxicology Review, general toxicology studies submitted as part of NDA 22374 submission are adequate. See March 26, 2010 NDA 22374 Clinical Review and the 2010 NDA 22374 and the 2012 current NDA 203585 Pharmacology/Toxicology Reviews.

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate. See section 5.3 for discussion and summary of clinical testing conducted. Safety concerns with omacetaxine include hematological (myelosuppression) and gastrointestinal (diarrhea, nausea, vomiting), and injection site reactions (given subcutaneous route of administration). The sponsor adequately monitored for these during scheduled visits.

7.2.5 Metabolic, Clearance, and Interaction Workup

The March 26, 2010 Clinical Review of NDA 22374 concluded the following (extracted from the 2010 Clinical Review):

Metabolism
In vitro: The metabolic stability study of omacetaxine in human liver microsomes suggested negligible disappearance of omacetaxine. As omacetaxine is a cephalotaxine ester, it is potentially susceptible to hydrolysis by esterase. Metabolic stability studies in human plasma indicated that approximately 15% and 20% of omacetaxine was lost after 30 minutes and 60 minutes incubation, respectively. The absence of the esterase inhibitor phenyl methanesulfonyl fluoride (PMSF) does not enhance the disappearance of omacetaxine from human liver microsomes, suggesting that liver esterases do not hydrolyze omacetaxine.

In vivo: The applicant claimed that omacetaxine was primarily metabolized by plasma esterase to the inactive metabolite DMHHT. However, the plasma exposure to DMHHT was only about 13% of plasma omacetaxine exposure. In addition, < 5% of an

administered omacetaxine dose was recovered as DMHHT in urine, and < 0.2% was recovered as cephalotaxine in urine. Due to the lack of a mass balance trial, the characterization of metabolites of omacetaxine in humans is incomplete.

Elimination
The major elimination route of omacetaxine is unknown. Study CGX-635-205 suggested that the urinary excretion of omacetaxine (12.4% on Day 1 and 14.6% on Day 11), DMHHT (4.1% on Day 1 and 4.9% on Day 11), and cephalotaxine (0.07% on day 1 and 0.14% on day 11). However, the total urinary excretion is unknown due to potential unidentified metabolites.

Clearance:
The estimated plasma clearance of omacetaxine was 24.0 ± 13.4 L/h on Day 1 and 19.0 ± 12.3 L/h on Day 11. Using data of 13 patients whose PK profiles were available for both Day 1 and Day 11, the mean ratio of (CL/F)Day11/(CL/F)Day1 was 0.93 with a 90% confidence interval (CI) of [0.70, 1.90]. The CL/F appears unchanged, though a conclusive decision can not be made due to wide confidence interval.

Half-life
The terminal half-life of omacetaxine was approximately six hours.

For additional detail, please see the Clinical Pharmacology Review/s (2010 NDA 22374 and 2012 NDA 203585).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Omacetaxine does not belong to an established pharmacologic class (EPC) at this time.

7.3 Major Safety Results

7.3.1 Deaths

There were 63 deaths of all causes (40% of subjects died), any time during trial with 34% of deaths in the CML-CP and 51% in the CML-AP group. A total of 17% of the deaths were due to disease progression. Table 22 summarizes the total number of deaths and **Error! Reference source not found.**Table 23 summarizes the causes of death.

Table 22 Total Deaths

	CML-CP n=103	CML-AP n = 55	Total n= 158
Number of deaths n (%)	35 (34)	28 (51)	63 (40)
Deaths during trial	4 (4)	4 (7)	8 (5)

Deaths during follow-up	31 (30)	24 (44)	55 (35)

Table 23 All-Cause Deaths Including Deaths > 30 Days From Last Dose

Cause of Death n (%)	CML-CP n=103	CML-AP n=55	Total n=158
Total deaths	35 (34)	28 (51)	63 (40)
Cardiac Arrest	1 (1)	0 (0)	1 (1)
Cerebral Hemorrhage	2 (2)	2 (4)	4 (3)
Complications of Allogeneic Bone Marrow Transplant	1 (1)	0 (0)	1 (1)
Failure to Thrive	1 (1)	0 (0)	1 (1)
Liver Failure	1 (1)	0 (0)	1 (1)
Multiorgan Failure	1 (1)	0 (0)	1 (1)
Neutropenic Fever	0 (0)	1 (2)	1 (1)
Pancytopenia	1 (1)	1 (2)	2 (1)
Pulmonary Hemorrhage	1 (1)	1 (2)	2 (1)
Sepsis	2 (2)	0 (0)	2 (1)
Disease Progression	15 (15)	12 (22)	27 (17)
Unknown	9 (9)	11 (20)	20 (13)

A total of 8 deaths occurred during trial, 4 in each group. Two of the 4 deaths in each group were due to cerebral hemorrhage. Table 24 Deaths During Trial**Error! Reference source not found.**summarizes the causes of deaths in each of the groups.

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Table 24 Deaths During Trial

CML-CP	
Patient ID	**Cause of Death**
CGX-635-CML-202/009/001	Cerebral Hemorrhage
CGX-635-CML-202/009/003	Unknown
CGX-635-CML-202/071/004	Cerebral Hemorrhage
CGX-635-CML-203/330/002	Multiorgan Failure
CML-AP	
Patient ID	**Cause of Death**
CGX-635-CML-202/050/001	Disease Progression
CGX-635-CML-203/301/014	Cerebral Hemorrhage
CGX-635-CML-203/320/004	Cerebral Hemorrhage
CGX-635-CML-203/371/002	Disease Progression

The following is a summary narrative of patients who died during trial in each group.

CML-CP
Patient CGX-635-CML-202/009/001 was a 62 year old White male with drug exposure of 496 days, who died of cerebral hemorrhage (b) (6) on trial, 18 days post last dose of drug. Cerebral hemorrhage started (b) (6); Date of death: (b) (6); Latest platelet count reported: 15.5 x 10^9 on 4/16/2009.

Patient CGX-635-CML-202/009/003 was a 57 year old White female with drug exposure of 125 days, who died of unknown cause (b) (6) on trial, 19 days post last dose of drug.

Patient CGX-635-CML-202/071/004 was a 40 year old Asian female with drug exposure of 14 days, who died of cerebral hemorrhage (b) (6) on trial, 18 days post last drug dose. Cerebral hemorrhage started (b) (6); Date of death: (b) (6) Latest platelet count reported was 40.0 x 10^9 on 1/12/2009.

Patient CGX-635-CML-203/330/002 was 69 year old White male with drug exposure of 7 days who died of multiorgan failure (b) (6) on trial, 17 days post last drug dose.

CML-AP
CGX-635-CML-202/050/001 was a 44 year old White female with drug exposure of 122 days who died of disease progression (b) (6) on trial, 23 days post last drug dose.

CGX-635-CML-203/301/014 was a 64 year old Black male with drug exposure of 40 days who died of cerebral hemorrhage (b) (6) on trial, 18 days post last drug dose. Cerebral hemorrhage started (b) (6); Date of death: (b) (6); Latest platelet count reported: 14.0 x 10^9 on 7/16/2008.

CGX-635-CML-203/320/004 was a 62 year old female non-Caucasian, non-Black, non-Asian, non-Hispanic ("other" race) with drug exposure of 37 days who died of cerebral hemorrhage (b) (6) on trial, 22 days since last drug dose. Cerebral hemorrhage started (b) (6); Date of death: (b) (6) Latest platelet count reported was 25.0 x 10^9 on 6/27/2009.

CGX-635-CML-203/371/002 was a 48 year old Asian female with drug exposure of 41 days who died of disease progression (b) (6) on trial, 18 days post last drug dose.

The major grade 3-4 adverse events were hematologic with thrombocytopenia being most common and the cause of most discontinuations due to hematologic toxicity.

There were 8 on-trial deaths (within 30 days), 4 in each group, with 2 of 4 deaths in each group due to cerebral hemorrhage. For all of these patients, platelet counts reported closest to the date of death were low, increasing the risk of serious bleeding.

7.3.2 Nonfatal Serious Adverse Events

The most frequently reported SAEs were febrile neutropenia (11%) and thrombocytopenia (10%) with febrile neutropenia more common in patients with CML-AP (20%) and thrombocytopenia more common in patients with CML-CP (11%). Table 25**Error! Reference source not found.** summarizes the SAEs.

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Table 25 Treatment Emergent Serious Adverse Events in ≥ 2 Patients

Preferred Term	CML-CP n=103	CML-AP n=55	Total n (%)
Febrile neutropenia	6 (6)	11 (20)	17 (11)
Thrombocytopenia	11 (11)	5 (9)	16 (10)
Pancytopenia	7 (7)	1 (2)	8 (5)
Anemia	2 (2)	4 (7)	6 (4)
Cerebral hemorrhage	2 (2)	2 (4)	4 (3)
Neutropenia	2 (2)	2 (4)	4 (3)
Pneumonia	2 (2)	2 (4)	4 (3)
Pyrexia	2 (2)	2 (4)	4 (3)
Diarrhea	0 (0)	3 (5)	3 (2)
Gastrointestinal hemorrhage	3 (3)	0 (0)	3 (2)
Back pain	2 (2)	0 (0)	2 (1)
Catheter sepsis	0 (0)	2 (4)	2 (1)
Fatigue	0 (0)	2 (4)	2 (1)

7.3.3 Dropouts and/or Discontinuations

The most common reasons for discontinuation were progressive disease (32%) and lack of efficacy (16%), with similar percentage of discontinuations for lack of efficacy among patients with CML-CP (17%) and CML-AP (15%) and more discontinuations due to progressive disease in patients with CML-AP (44% versus 26%) as summarized in Table 26 Treatment emergent adverse events leading to drug discontinuation were hematological (thrombocytopenia [11%], followed by pancytopenia [3%]), as listed in, Table 27 below.

Table 26 Reasons for Discontinuations

Reason for discontinuations n (%)	CML-CP n=103	CML-AP n=55	Total n = 158
Total Number of Patients Discontinued	86 (83)	52 (95)	138 (87)
Treatment Emergent Adverse Event Thrombocytopenia	10 (10) 2 (2)	7 (13) 3 (5)	17 (11) 5 (3)
Death	8 (8)	5 (9)	13 (8)
Progressive Disease	27 (26)	24 (44)	51 (32)
Lack of Efficacy	17 (17)	8 (15)	25 (16)
Loss to Follow-up	1 (1)	1 (2)	2 (1)
Non-compliance with Study Drug	1 (1)	0 (0)	1 (1)
Withdrawal by Subject	12 (12)	5 (9)	17 (11)
Other	9 (9)	2 (4)	11 (7)

Table 27 Treatment Emergent Adverse Events Leading To Discontinuation

	CML-CP n (%) n=103	CML-AP n (%) n=55	Total n (%) n=158
Total patients with ≥1 TEAS leading to D/C	10 (10)	7 (11)	17 (11)
Thrombocytopenia	2 (2)	3 (5)	5 (3)
Pancytopenia	2 (2)	0 (0)	2 (1)
Alanine Aminotransferase Increase	2 (2)	0 (0)	2 (1)
Bone Marrow Failure	0 (0)	1 (2)	1 (1)
Tachyarrhythmia	1 (1)	0 (0)	1 (1)
Diplopia	1 (1)	0 (0)	1 (1)
Pneumonia	0 (0)	1 (2)	1 (1)
Sepsis	1 (1)	0 (0)	1 (1)
Multiorgan failure	0 (0)	1 (2)	1 (1)
Gout	1 (1)	0 (0)	1 (1)
Renal Failure	0 (0)	1 (2)	1 (1)

7.3.4 Significant Adverse Events

Myelosuppression, including grade 3-4 thrombocytopenia, anemia, and neutropenia, as listed below in Table 28, are significant adverse events seen, with grade 3-4 anemia occurring at a similar rate in both groups (CP 37% compared to AP 38%), grade 3-4 thrombocytopenia higher in the CP group (68%) than in the AP group (51%), and neutropenia grade 3-4 higher in the CP group (47%) compared to in the AP group (20%).

Reviewer comment: The higher rate of hematologic adverse events in the CP suggests a relationship to drug exposure as the patients with CML-CP had a higher median exposure to drug than patients with CML-AP (7.6 versus 1.9 months) and higher median drug exposure (132.8 mg/m^2 versus 69.6 mg/m^2, respectively).

Table 28 Hematological Treatment Emergent Adverse Events

	CML-CP		CML-AP	
	All Grades	Highest Grade	All Grade	Highest Grade
Thrombocytopenia	75%	68% grade 3-4	58%	51% grade 3-4
Anemia	63%	37% grade 3-4	54%	38% grade 3-4
Neutropenia	52%	47% grade 3-4	22%	20% grade 3-4

Table 29 Non-Hematological Treatment Emergent Adverse Events

	CML-CP		CML-AP	
	All Grades	Highest Grade	All Grade	Highest Grade
Injection site erythema	18%	100% Grade 1-2	11%	100% Grade 1-2
Diarrhea	44%	1% Grade 3-4	31%	9% Grade 3-4
Nausea	33%	1% Grade 3-4	29%	4% Grade 3-4
Vomiting	12%	100% Grade 1-2	18%	4% Grade 3-4
Fatigue/Asthenia	52%	5% Grade 3-4	44%	5% Grade 3
Pyrexia	24%	1% Grade 3-4	29%	2% Grade 3-4
Hyperglycemia	66%	11% Grade 3-4	58%	16% Grade 3-4
Upper Respiratory Tract Infection	11%	11% Grade 1-2	5%	5% Grade 1-2
Pneumonia	3%	3% Grade 3-4	13%	7% Grade 3-4

7.3.5 Submission Specific Primary Safety Concerns

(b) (4)

The Agency reviewed the proposal and identified serious safety concerns with this plan.

(b) (4)

The originally proposed tradename Omasona was not acceptabl (b) (4) . See the June 28, 2012 DMEPA Proprietary Name Review. The applicant has thus proposed the trade name Synribo for consideration; the newly proposed trade name Synribo is currently under DMEPA review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common treatment emergent adverse events of any grade included hematologic (myelosuppressive) adverse events, mainly thrombocytopenia, anemia and neutropenia, GI adverse events, mostly diarrhea and nausea, and fatigue (fatigue/asthenia). There were few injection site reactions and they were typically low grade Table 30 below summarizes the safety analysis for treatment emergent adverse events occurring in ≥10% of subjects with CML-CP and Table 31 below summarizes the safety analysis for treatment emergent adverse events occurring in ≥10% of subjects with CML-AP.

Table 30 CML-CP Treatment Emergent Adverse Events in ≥ 10% of Patients

	CML-CP Total Patients n=103		
Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**
All patients with ≥ 1 adverse event	102 (99)	76 (74)	52 (50)
Thrombocytopenia	77 (75)	70 (68)	36 (35)
Anemia	65 (63)	38 (37)	5 (5)
Neutropenia	54 (52)	48 (47)	25 (24)
Diarrhea	45 (44)	1 (1)	0 (0)
Nausea	34 (33)	1 (1)	0 (0)
Fatigue/Asthenia	54 (52)	5 (5)	0 (0)
Pyrexia	25 (24)	1 (1)	0 (0)
Arthralgia	19 (18)	1 (1)	0 (0)
Headache	19 (18)	1 (1)	0 (0)
Injection Site Erythema	19 (18)	0 (0)	0 (0)
Lymphopenia	18 (17)	16 (16)	4 (4)
Constipation	17 (17)	0 (0)	0 (0)
Epistaxis	17 (17)	1 (1)	1 (1)
Cough	16 (16)	1 (1)	0 (0)
Pain in Extremity	15 (15)	1 (1)	0 (0)
Peripheral Edema	15 (15)	0 (0)	0 (0)
Alopecia	15 (15)	0 (0)	0 (0)
Abdominal Pain, Upper	15 (15)	0 (0)	0 (0)
Febrile Neutropenia	12 (12)	12 (12)	4 (4)
Back Pain	12 (12)	2 (2)	0 (0)
Vomiting	12 (12)	0 (0)	0 (0)
Rash	11 (11)	0 (0)	0 (0)
Insomnia	11 (11)	0 (0)	0 (0)
Upper Respiratory Tract Infection	11 (11)	0 (0)	0 (0)

Table 31 CML-AP Treatment Emergent Adverse Events in ≥ 10% of Patients

	CML-AP Total Patients n=55		
Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**Grade 4 n (%)**
All patients with ≥ 1 adverse reaction	55 (100)	38 (69)	25 (45)
Thrombocytopenia	32 (58)	28 (51)	22 (40)
Anemia	29 (54)	21 (38)	8 (15)
Diarrhea	17 (31)	5 (9)	0 (0)
Pyrexia	16 (29)	1 (2)	0 (0)
Fatigue/Asthenia	24 (44)	3 (5)	0 (0)
Nausea	16 (29)	2 (4)	0 (0)
Febrile Neutropenia	12 (22)	9 (16)	2 (4)
Neutropenia	12 (22)	11 (20)	7 (13)
Vomiting	10 (18)	2 (4)	0 (0)
Abdominal Pain	9 (16)	0 (0)	0 (0)
Cough	9 (16)	0 (0)	0 (0)
Pain in Extremity	8 (15)	1 (2)	0 (0)
Anorexia	7 (13)	1 (2)	0 (0)
Chills	7 (13)	0 (0)	0 (0)
Headache	7 (13)	0 (0)	0 (0)
Peripheral Edema	7 (13)	0 (0)	0 (0)
Pneumonia	7 (13)	4 (7)	0 (0)
Arthralgia	6 (11)	0 (0)	0 (0)
Bronchitis	6 (11)	0 (0)	0 (0)
Dyspnea	6 (11)	1 (2)	0 (0)
Epistaxis	6 (11)	1 (2)	0 (0)
Injection Site Erythema	6 (11)	0 (0)	0 (0)

In the CML-CP population, 99% of patients had at least 1 adverse event. The most frequently occurring adverse events were hematological, with thrombocytopenia being the most common (75%) followed by anemia (63%), and neutropenia (52%). Other common adverse events included gastrointestinal disorders, with diarrhea being the most common (44%), followed by nausea (33%). Asthenia/fatigue was the other most common adverse event (52%).

In the CML-AP population 100% of patients had at least 1 adverse event. The most frequently occurring adverse events were hematological, with thrombocytopenia being the most common (58%) followed by anemia (54%); neutropenia occurred in 22% of patients in CML-AP group. Other common adverse events included gastrointestinal disorders, with diarrhea being the most common (32%); nausea occurred in 29%. Asthenia/fatigue was the other most common adverse event (44%).

7.4.3 Vital Signs

Vital signs measurements were not reported in study 04.2/04.3. For trials CML-202 and CML-203, overall, there were no changes of any clinical significance from baseline to highest post-baseline value or from baseline to lowest post-baseline value in systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, temperature, or weight, in any phase of either population.

7.4.4 Electrocardiograms (ECGs)

The following is extracted from the QT-IRT review for NDA 203585: "The Sponsor submitted a concentration-QT report using data from study CGX-635-205. QT-IRT previously performed an independent review of this data in the original review under NDA22374 dated December 15, 2009. There is no new evidence or data to change the overall conclusions noted in the previous review. We therefore refer the Division to the original review for QT-IRT conclusions and recommendations, including suggested labeling language".

The following is extracted from the QT-IRT review for NDA 22374:
"In this open-label, non-randomized pharmacokinetic study, 21 patients with relapsed or refractory hematologic malignancies or advanced solid tumors with no bone marrow involvement received omacetaxine 1.25 mg/m2 sc BID for 14 consecutive days, followed by two weeks off drug and a repeat of the treatment cycle. Following the first dose, the largest upper bound of the 2-sided 90% CI for the mean difference between omacetaxine (1.25 mg/m2 BID) and baseline was 4.2 ms (upper 95% CI: 9.5 ms) at 8 hours. QTc effects less than 10 ms cannot be verified in the absence of a placebo and positive controls. None of the 21 patients had QTcF > 480 ms or ΔQTcF > 60 ms following omacetaxine administration. There was no evidence for concentration-dependent increases in QTc for omacetaxine or 4'-DMHHT. Overall, no substantial QT-prolonging effects of omacetaxine were detected for 12-hours following a single sc dose."

The overall summary of conclusions of QT-IRT consult is that in the pharmacokinetic study described above, there were no reports of QTcF > 480 ms or ΔQTcF > 60 ms and no evidence for concentration-dependent increases in QTc for omacetaxine or 4'-DMHHT. Also, although the mean effect on QTc was 4.2 ms (upper 95% CI: 9.5 ms), QTc effects less than 10 ms could not be verified due to the absence of a placebo and positive controls.

Please also see Clinical Pharmacology Review.

7.4.5 Special Safety Studies/Clinical Trials

(b) (4)

(b) (4)

7.4.6 Immunogenicity

No specific immunogenicity studies were conducted for this NDA submission.

Hypersensitivity reactions were reported in 3% (3/103) of the safety population, all of which were grade 1-2 (1/103) allergic dermatitis in patients with CML-CP. There was 1 grade 1 hypersensitivity reaction (1/55), and 1 (1/55) grade 2 allergic dermatitis, and 1 grade 1 (1/55) exfoliative rash in patients with CML-AP.

7.5 Other Safety Explorations

Adverse events of special interest
The following were events of special interest, per the applicant, based on historical findings and mechanism of action of the study drug: arrhythmia, hematotoxicity, hyperbilirubinemia, hyperglycemia, hypotension, injection site reaction, infections, as follows:

CML-CP
Hematological:
- Thrombocytopenia: 74% (72% related to study drug; 67% grade 3-4 including the 66% of grade 3-4 related to study drug)
- Anemia: 61% (59% related to study drug; 36% grade 3-4 including the 35% of grade 3-4 related to study drug)
- Neutropenia: 50% (all related to study drug; 45%grade 3-4)
- Febrile neutropenia: 10% (all grade 3-4 of which 8% was related to study drug)

Arrhythmia: 2%
Hypotension: 2% (1% related to study drug)
Injection site erythema: 19% (all related to study drug)
Hyperbilirubinemia 6% (5% related to study drug)
Hyperglycemia: 7% (5% related to study drug; 1% grade 3-4)
Hyperglycemic hyperosmolar non-ketoacidotic syndrome: 1% (related; grade 3-4)
Pneumonia: 3% (all grade 3-4 of which 1% was related to study drug)
Upper respiratory tract infection: 11% (2% related to study drug)
Urinary tract infection: 5% (1% related to study drug)
Herpes zoster: 4%
Gastritis: 4%

CML-AP

Hematological
Thrombocytopenia: 57% (51% related to study drug; 49% grade 3-4 including the 46% of grade 3-4 related to study drug)
Anemia: 51% (42% related to study drug; 36 grade 3-4 including the 33% of grade 3-4 related to study drug)
Neutropenia: 20% (all related to study drug; 18% grade 3-4)
Febrile neutropenia: 20% (16% related and grade 3-4)
Hypotension: 2%
Hyperbilirubinemia: 4% (all related to study drug; 2% grade 3-4)
Hyperglycemia: 4% (all related to study drug; 2% grade 3-4)
Injection site erythema: 11% (all related to study drug)
Pneumonia: 11% (7% grade 3-4; 4% related, including 1% of the grade 3-4)
Upper respiratory tract infection: 5%
Urinary tract infection: 6%
Herpes Zoster: 2% (2% grade 3-4)

Overall the incidence of arrhythmia and hypotension were low with 2% incidence reported in patients with CML-CP and none in the CML-AP safety populations. Injection site erythema was of lower grade (none were grade 3-4), and infections were of low incidence and fewer considered related to the study drug. Hyperglycemia was typically of low grade (only 1% were grade 3-4) and 5% and 4% related to study drug in CML-CP and CML-AP respectively. As pertains to hyperosmolar hyperglycemia, one case of grade 3 hyperglycemia with hyperosmolar coma at 3 mg/m^2 was reported in a publication by Levy et al. in a dose finding trial for homoharringtonine.[2]

Hematologic adverse events of interest were, as expected, the highest in incidence among adverse events of interest, with thrombocytopenia being the most common in both CML-CP and CML-AP groups and most hematologic adverse events related to study drug, as described above.

7.5.1 Dose Dependency for Adverse Events

The trial population was very small and only a single dose level of 1.25 mg/m^2 was explored. Dose modifications for toxicity were permitted. This trial design renders determination of dose dependency of adverse events impossible, as previously concluded in the March 26, 2010 clinical review of NDA 22374.

7.5.2 Time Dependency for Adverse Events

Patients received 14-day induction cycles followed by 7-day maintenance cycles if their disease responded to therapy and they remained on the trial. Patients whose disease did not respond or progressed on therapy were removed from the trial and did not receive maintenance courses. Overall, patients received a median of 5 cycles of therapy with 20% of patients discontinuing therapy by cycle 1 (17% in CML-CP and 27% in

CML-AP). The most common reason for discontinuation was disease progression (26% in CML-CP and 44% in CML-AP). The most common adverse events leading to drug discontinuation was thrombocytopenia (2% in CML-CP and 5% in CML-AP)

7.5.3 Drug-Demographic Interactions

Differential Safety by Age

Patients with Chronic Phase CML:

In the CP-CML patients, the following adverse events were reported more frequently in patients 65 years and older than in patients less than 65 years: anemia (83% vs 53%), lymphopenia (24% vs 14%), upper abdominal pain (28% vs 9%), asthenia (35% vs 19%), bone pain (17% vs 4%), pain in extremity (24% vs 9%), insomnia (17% vs 8%), and Epistaxis (24% vs 11%).

Several events were reported more frequently in patients less than 65 years and older than in patients less than 65 years. Those included febrile neutropenia (11.4% vs 6.9%), vomiting (15.2% vs 3.4%), pyrexia (27.8% vs 13.8%), myalgia (11.4% vs 3.4%), and headache (20.3% vs 13.8%).

Patients with Accelerated Phase CML:

Among patients with AP-CML the following AEs were reported more frequently in patients 65 years and older than in patients less than 65: neutropenia (35.0% vs 11.4%), thrombocytopenia (65.0% vs 51.4%), diarrhea (45.0% vs 28.6%), asthenia (40.0% vs 14.3%), pneumonia (20.0% vs 5.7%), pain in extremity (25.0% vs 2.9%), cough (25.0% vs 8.6%), and dyspnea (25.0% vs 2.9%).

There were no notable events in the Accelerated Phase patients that had a higher incidence in patients less than 65 years than in patients 65 years and older.

Differential Safety by Gender

Patients with Chronic Phase-CML

In the population of patients in chronic phase, there were 68 men and 40 women. Among the patients with CP-CML, the following adverse events were reported more frequently in women than in men: febrile neutropenia (15.0% vs 7.4%), abdominal pain (20.0% vs 2.9%), vomiting (27.5% vs 2.9%), injection site erythema (32.5% vs 11.8%), peripheral edema (22.5% vs 7.4%), arthralgia (27.5% vs 13.2%), headache (30.0% vs 11.8%), alopecia (22.5% vs 10.3%), and hypertension (15.0% vs 1.5%)

In the same population, the following adverse events were reported more frequently in men than in women: bone marrow failure (14.7% vs 2.5%), thrombocytopenia (77.9% vs 67.5%), increased alanine aminotransferase (11.8% vs 2.5%), and epistaxis (19.1% vs 7.5%).

Patients with Accelerated Phase-CML

In the population of patients in accelerated phase, there were 34 men and 21 women. Among the patients with AP-CML the following adverse events were reported more frequently in women than in men: anemia (61.9% vs 44.1%), febrile neutropenia (33.3% vs 11.8%), neutropenia (33.3% vs 11.8%), diarrhea (42.9% vs 29.4%), nausea (38.1% vs 20.6%), asthenia (38.1% vs 14.7%), and pyrexia (33.3% vs 26.5%).

In the same population, the following events had a higher incidence in men than in women: fatigue (41.2% vs 14.3%) and epistaxis (14.7% vs 4.8%).

Differential Safety by Race

Patients with CP-CML

Among the patients with CP-CML, there were 79 white patients and 29 non-white patients. The following AEs were reported more frequently in white patients than in non-white patients: anemia (69.6% vs 37.9%), diarrhea (44.3% vs 34.5%), fatigue (31.6% vs 10.3%), and peripheral edema (16.5% vs 3.4%).

There were no notable events that had a higher incidence in non-white patients than in white patients.

Patients with AP-CML

Among the patients with AP-CML, there were 29 white patients and 26 non-white patients. The following AEs were reported more frequently in non-white patients than in white patients: febrile neutropenia (30.8% vs 10.3%), diarrhea (38.5% vs 31.0%), and fatigue (46.2% vs 17.2%)

7.5.4 Drug-Disease Interactions

No drug-disease interaction studies/trials were conducted.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies/trials were conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies are not required in the TKI resistant/intolerant CML population and were not conducted in humans. See the Pharmacology/Toxicology review.
The March 26, 2010, clinical review of NDA 22374 concluded there is no conclusive evidence for risk of carcinogenicity due to omacetaxine. See the March 26, 2010, NDA 22374 Clinical Review.

7.6.2 Human Reproduction and Pregnancy Data

No reproduction and pregnancy studies were conducted in humans. Pregnant and breast-feeding women were excluded from the clinical trials. Results from studies in mice indicate embryolethality potential. The following is extracted from the Pharmacology Toxicology Review for NDA 203585 (amendment to NDA 22374 Pharmacology Toxicology Review): Genotoxicity results were negative in Ames test *in vivo* mouse micronucleus assay, but were positive in chromosomal aberration assay *in vitro*. Using a plate incorporation method, omacetaxine did not induce genotoxic responses in bacteria, with or without S9 metabolic activation. This study used the highest concentration recommended by ICH S2(R1) (5.0 mg/plate), and the results are considered valid and adequate.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric age group patients were enrolled in the clinical trials submitted.

Extracted from March 26, 2010 clinical review of NDA 22374: Omacetaxine was granted orphan drug designation for treatment of patients with CML in March 10, 2006 exempting it from the requirements of the Pediatric Research Equity Act (PREA). Data from pediatric studies has therefore not been submitted by the applicant. However studies in patients with leukemia have been previously reported from China and North America. These studies were in small groups of acutely ill patients and no long term data are available regarding the effects of this agent on growth and development. [3,4]

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

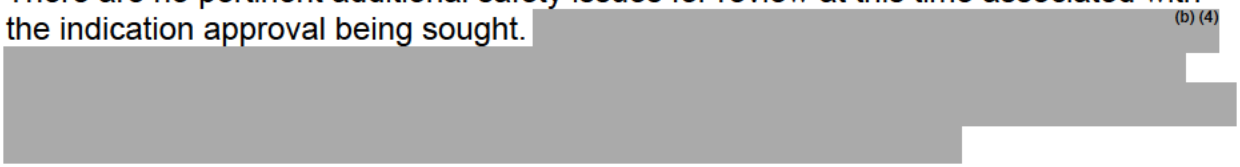
Omacetaxine has been administered subcutaneously to patients with leukemia at the 1.25 mg/m^2 and 2.5 mg/m^2 (twice a day) dose levels in patients with CML and AML, respectively. At both dose levels, the adverse event profile of the drug was similar, with myelosuppression being the predominant toxicity. There are no specific signs, symptoms, or laboratory findings that were reported at the 2.5 mg/m^2 dose level.

In light of these findings, the consequences of overdosing in the CML patient population is expected to be limited to myelosuppression. A small number of accidental overdose/dosing errors were reported in clinical studies of omacetaxine. A patient with CML in the expanded access program received a dose of 2.5 mg/m^2 twice daily for 5 days due to a reconstitution error. The patient presented with gastrointestinal disorders, gingival hemorrhage, alopecia, and grade 4 thrombocytopenia and neutropenia. When omacetaxine was discontinued, the gastrointestinal disorders and hemorrhagic syndrome resolved and blood counts returned to grade 1 or better. Alopecia also improved.

There is no known antidote to reverse the effects of an overdose of omacetaxine. Patients who receive an overdose should be monitored closely for heightened adverse events related to myelosuppression and gastrointestinal toxicity.

7.7 Additional Submissions / Safety Issues

There are no pertinent additional safety issues for review at this time associated with the indication approval being sought.



Additional information was received in the form of safety updates. A safety update submitted on 07/27/2012 by the applicant, does not alter the safety profile of the drug and does not raise new safety concerns.

8 Postmarket Experience

There is no postmarket experience with this new molecular entity.

9 Appendices

9.1 Literature Review/References

1. European Medicines Agency. European public assessment reports. Retrieved September 2, 2012, from http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001244/wapp/Initial_authorisation/human_wapp_000112.jsp&mid=WC0b01ac058001d128&source=homeMedSearch&category=human

2. Levy V, Zohar S, Bardin C, Vekhoff A, Chaoui D, Rio B, et al. A phase I dose-finding and pharmacokinetic study of subcutaneous semisynthetic homoharringtonine (ssHHT) in patients with advanced acute myeloid leukaemia. *Br J Cancer* 2006;95(3):253-9.

3. Tan CTC, Luks E, Bacha DM et al. Phase I Trial of Homoharrington in Children With Refractory Leukemia. *Cancer Treat Rep* 1987; 71:1245-1248.

4. Bell BA, Chang MN, Weinstein HJ. A Phase II Study of Homoharringtonine for the Treatment of Children With Refractory or Recurrent Acute Myelogenous Leukemia: A Pediatric Oncology Group Study. *Med Pediatr Oncol* 2001;37:103-107.

5. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science* 2004;305(5682):399-401.

6. Corters J. et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation. *Blood* 2012 (August 15, 2012 (Epublication)

7. Sylvester RK. et al. Homoharringtonine-induced hyperglycemia. *J Clin Oncol.* 1989 Mar;7(3):392-5.

8. National Comprehensive Cancer Network (NCCN) Practice Guidelines Version 1.2013 Chronic Myelogenous Leukemia from http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf

9. Fialkow, P. J., Jacobson, R. J., and Papayannopoulou, T. Chronic myelocytic leukemia: clonal origin in a stem cell common to the granulocyte, erythrocyte, platelet, and monocyte/macrophage. *Am. J. Med.* 1997; 63*:* 125–130.

9.2 Labeling Recommendations

The proposed labeling by the applicant [redacted] was found inadequate for the indication: "*Tradename for Injection 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) including imatinib, dasatinib or nilotinib.*" The sponsor was advised of the concerns of exposure risk and risk of incorrect dosing [redacted] and a recommendation was made that the drug, if approved, be reconstituted and administered in the clinical setting. Thus, following a teleconference between FDA and Teva Pharmaceuticals Ltd. (Cephalon, Inc.) on July 31, 2012, the applicant revised the labeling. The revised labeling provides for reconstitution and administration in a health care setting. [redacted]

The applicant also revised the indication, after discussion with FDA, to clarify that the drug was intended for use as third (or greater) line therapy of CML.

The revised proposed label was reviewed. The revisions reflect [redacted] clarification of the indication as third or greater line therapy as follows: "*TRADENAME for Injection 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 two or more tyrosine kinase inhibitors (TKI).*"

The changes made to the label by the Agency include efficacy and safety portions of the label as follows:

- Exclusion of those patients from the efficacy evaluable and safety evaluable populations for whom data was deemed unreliable as a result of major findings of the site inspections (sites 22 and 30)
- Exclusion from the efficacy evaluable of those patients who were deemed by the DMC as having entered the trial with best response

The Agency recommends inclusion of the efficacy data reflecting exclusion of those subjects with best response at trial entry as per the table below:

Table 32 Efficacy

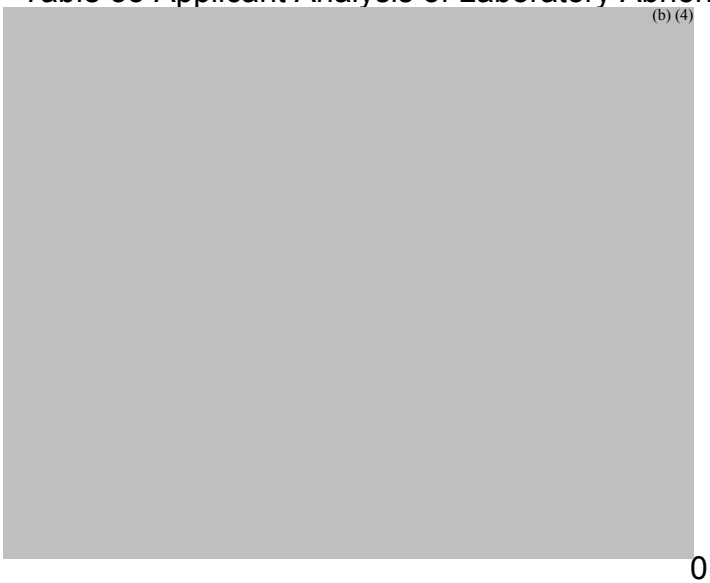
	Chronic phase (N = 76)	**Accelerated phase (N = 35)**
Responders*		
n, % (95% confidence interval)	14, 18.4% (10.5% - 29.0%)	5, 14.3% (4.5% - 30.3%)
Time to Onset of Response (months)[1]		
Mean, Median	3.5, 2.8	2.3, 2.5
Minimum, Maximum	1.2, 6.3	1.0, 4.2
Duration of Response (Months)[1]		
Median	12.5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

Source: FDA Statistics Review

As pertains to the safety data reported in the label, as the analyses from the applicant including 5 patients from sites 22 and 30 are very similar (within 1-2%) to the analysis excluding these patients, the currently proposed safety data in the label is adequate.

It is also recommended that a list of adverse events in <10% of the trial population be removed (Section 6.2 in the proposed August 10, 2012 label, submitted by the applicant on August 14, 2012). Laboratory abnormalities were different from that proposed by the applicant. The FDA laboratory abnormality analysis excludes from the denominator 7 patients in the CML-CP and 5 patients in the CML-AP group who did not have complete laboratory data, which may explain the differences the applicant and FDA analyses as presented in Table 33 and Table 34 below, respectively.

Table 33 Applicant Analysis of Laboratory Abnormalities



012) - *Section 6.1*.

Table 34 FDA Analysis of Laboratory Abnormalities

	CML-CP n=101*		CML-AP n=50*	
Lab n (%)	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
ALT increase	49 (49)	5 (5)	25 (50)	1 (2)
Bilirubin increase	44 (44)	9 (9)	17 (34)	4 (8)
Creatinine increase	32 (32)	8 (8)	18 (36)	7 (14)
Hb decrease	87 (84)	60 (59)	44 (88)	37 (74)
Hyperglycemia	67 (66)	11 (11)	29 (58)	8 (16)
Hyperuricemia	39 (39)	39 (39)	18 (36)	18 (36)
Hypoglycemia	18 (18)	7 (7)	6 (12)	3 (6)
Neutrophils Decrease	88 (87)	79 (78)	36 (72)	30 (60)
Platelet Decrease	88 (87)	80 (79)	37 (74)	33 (66)

As for the differences in subgroups and special populations reported in the label for the efficacy and safety population, it is recommended that a statement be included indicating that the numbers of the subgroups (numbers of patients with the corresponding parameters discussed) are too small to make meaningful clinical conclusions and these analyses should be considered exploratory. See also Labeling Review.

No additional labeling recommendations are deemed necessary from the clinical perspective.

Reviewer comment: *FDA recommendation for labeling is that the efficacy results presented in the label should reflect analyses done using data that excludes 3 subjects from sites 22 and 30 and 8 subjects who entered the trial in baseline best response. The safety results are similar between the analyses of the applicant and the FDA which excludes patients from sites 22 and 30 (a total of 5 subjects who had at least one dose of SC omacetaxine mepesuccinate, 2 of whom did not meet criteria for selection for inclusion in efficacy Analysis CML-300. There are differences in incidences of laboratory abnormalities between the applicant and FDA analyses, which may be due to the different number of subjects included (as those subjects for whom laboratory information was missing were not included in the total by FDA analysis, in an effort to minimize underestimation of those abnormalities). Furthermore, the applicant's proposed rates of adverse events are based on analyses that allowed for attribution of adverse events. The Agency does not allow for attribution when analyzing the safety of an NME evaluated in single arm trials. The FDA analysis of laboratory abnormalities should replace that of the applicant in the label.*

The drug, (b) (4) is to be prepared and administered by a healthcare professional in a healthcare setting.

9.3 Advisory Committee Meeting

Omacetaxine was previously discussed at an advisory committee meeting. No new issues were identified that would require additional public discussion so no advisory committee was necessary for this NDA submission.

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/s/

FIROOZEH ALVANDI
09/21/2012

VIRGINIA E KWITKOWSKI
09/21/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 203585 **Applicant: Cephalon Pharmaceuticals Inc.** **Stamp Date: March 30, 2012**

Drug Name: omacetaxine mepesuccinate for injection **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			Electronic eCTD submission
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			Applicant seeks indication for omacetaxine mepesuccinate for injection for the treatment of adult patients with chronic or accelerated phase chronic myelogenous leukemia with resistance and/or intolerance to prior tyrosine kinase inhibitors including imatinib, dasatinib or nilotinib
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b) (1) or a 505(b) (2). If Application is a 505(b) (2) and if appropriate, what is the reference drug?	x			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number:	x			The applicant relied on trials by Levy et al. *British Journal of Cancer* (2006) 95, 253 – 259 and cited also Feldman et al. *Leukemia* 1992;6:1185-1188 for an

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study Title: Sample Size: Arms: Location in submission: 5.3.3 – Applicant relied on published trials by Levy et al. *British Journal of Cancer* (2006) 95, 253 – 259 and cited also Feldman et al. *Leukemia* 1992;6:1185-1188.				MTD of 5mg per m^2 per day .
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **Analysis CGX-635-CML-300** Subset analysis of patients (122 patients) with prior TKI refractoriness/ intolerance from two trials (CGX-635-CML-202, CGX-635-CML-203) Pivotal Trial # 1 CGX-635-CML-202 Phase II Open-Label Study of the Subcutaneous Administration of Homoharringtonine (Omacetaxine) (CGX-635) in the Treatment of Patients with Chronic Myeloid Leukemia (CML) With the T315I Bcr-Abl Gene Mutation (103 patients) Pivotal Trial #2 CGX-635-CML-203 A Phase II Open-Label Study of the Subcutaneous Administration of Homoharringtonine (Omacetaxine Mepesuccinate) in the Treatment of Patients With Chronic Myeloid Leukemia (CML) Who Have Failed or are Intolerant to Tyrosine Kinase Inhibitor Therapy (100 patients)	x			Label indication sought: 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
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			Analysis CML-300
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			Applicant conducted a new exploratory concentration vs. QT analysis Trial PC-11-008 – Concentration QTc IRT will review finding. Trial CGX-635-205 – Per prior clin pharm and IRT review (at time of NDA 22374 review), it was concluded that no substantial QT

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					prolonging effects of omacetaxine were detected. However, QTc effects less than 10 ms can not be verified in the absence of placebo and positive controls.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Waiver - Omacetaxine mepesuccinate has orphan drug designation for use in patients with CML (Orphan Designation 05-2182).
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____ Yes**____**

If the Application is not fileable from the clinical 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.

Firoozeh Alvandi, MD 5/08/2012

Reviewing Medical Officer Date

Virginia, Kwitkowski, MS, RN, ACNP-BC 5/10/2012

Clinical Team Leader Date

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

/s/

FIROOZEH ALVANDI
05/10/2012

VIRGINIA E KWITKOWSKI
05/11/2012