CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203585Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 2, 2012
From	Virginia Kwitkowski, MS, RN, ACNP-BC
Subject	Cross-Discipline Team Leader Review
NDA #	203585 / 0
Applicant	Cephalon (a wholly owned subsidiary of Teva Pharmaceutical Industries, Ltd.)
Date of Submission	March 30, 2012
PDUFA Goal Date	January 30, 2013
Proprietary Name / Established (USAN) names	SYNRIBO Omacetaxine mepesuccinate
Dosage forms / Strength	Lyophilized powder for reconstitution
Proposed Indication(s)	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.
Recommended:	*Accelerated Approval*

1. Introduction

Cephalon has submitted a new drug application under the 505(b)(1) regulations for omacetaxine mepesuccinate.

The proposed indication 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."*

Omacetaxine mepesuccinate is a new molecular entity. Omacetaxine does not belong to an established pharmacologic class. The mechanism of action 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 semi synthetic 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.

The application contained a combined subset of patients from two single-arm trials. This was considered acceptable to the Division because all of the previous applications for relapsed/refractory CML indications have contained a single trial. CML is a rare disease with approximately 5430 patients diagnosed in the U.S. per year[1]. The Application was filed as a standard review designation. DHP designated the application as standard review because the indication, as drafted, appeared to request a second-line indication because as worded, failure of only one prior TKI would allow treatment with omacetaxine. Because the data provided does not justify an indication for after one TKI and there are agents approved in the second-line indication with regular approval, the Division decided that the patients had other available therapies and that the application should be reviewed under 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. The PDUFA date was not changed to reflect PRIORITY review because per CDER MaPP 6020.30, "after it is assigned at the time of filing, the review timeline will not change during the first review cycle, even if a redetermination of review status were made because of the approval of other drugs or the availability of new data." However, the Division did agree to attempt to expedite the review of the application as much as possible.

Omacetaxine mepesuccinate was previously submitted by Chemgenex [the previous Applicant] to the agency under NDA 22374 in November 2009. At that time, the proposed indication was 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).

This product 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). Please refer to the Summary Review for Regulatory Action authored by Robert Justice, MD, Division Director of DOP1, for the rationale behind the decision to issue a Complete Response action.

A pre-NDA meeting was held on June 30, 2010 with Chemgenex 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).

NDA 22347 was subsequently withdrawn in February of 2011. Cephalon also acquired Chemgenex in 2011. 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 2 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.

2. Background

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.

Prior to 2001, CML was managed with agents like busulfan, hydroxyurea, interferon alpha, and allogeneic bone marrow or stem cell transplantation.

Approval of Gleevec
The 2001 U.S. approval of imatinib (Gleevec ®) revolutionized the treatment of CML in this country and provided the first tyrosine kinase inhibitor (TKI) for use in patients with newly diagnosed Chronic Phase (CP) CML based upon the results from the randomized phase 3 IRIS trial.

Approval of Sprycel
On June 28, 2006, the FDA granted accelerated approval to dasatinib (Sprycel) for the treatment of adults with chronic myeloid leukemia [CP-CML, AP-CML, and BP-CML] with resistance or intolerance to prior therapy including imatinib. This approval was based upon at least 12 months follow-up of all patients. As a condition of accelerated approval, the Applicant was required to submit 24 month follow-up data from the original Phase 2 trial. On May 21, 2009 the FDA converted the accelerated approval to regular approval based upon 24 months of follow-up data submitted by the Applicant. On October 28, 2010, the FDA approved dasatinib, for the treatment of newly diagnosed adult patients with CML-CP, with a recommended dose of 100 mg/day.

Approval of Tasigna
On October 29, 2007, FDA granted accelerated approval for nilotinib (Tasigna) "for chronic phase (CP) and accelerated phase (AP) Philadelphia positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to prior therapy that included Gleevec ® (imatinib)". This approval was based upon at least 12 months follow-up of all patients. As a condition accelerated approval, the Applicant was required to submit 24 month follow-up data from the original Phase 2 trial.

On June 17, 2010, the accelerated approval was converted to regular approval based upon 24 months of follow-up data submitted by the Applicant. At the same time, nilotinib was granted accelerated approval by the FDA for the treatment of adult patients with newly diagnosed CP-CML based upon a randomized trial comparing nilotinib to imatinib in patients with newly diagnosed chronic phase CML. The recommended nilotinib dose for the newly diagnosed patients is 300 mg by mouth twice daily. The recommended nilotinib dose for patients with

CML that is resistant or intolerant to imatinib is 400 mg by mouth twice daily. Nilotinib also has regular approval for the treatment of accelerated phase CML in adult patients resistant to or intolerant to prior therapy that included imatinib.

Approval of Bosulif
On September 4, 2012, bosutinib was granted regular approval for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance, or intolerance to prior therapy. This approval was a second-line indication and regular approval was granted because the Applicant submitted data that included 24 months of follow-up.

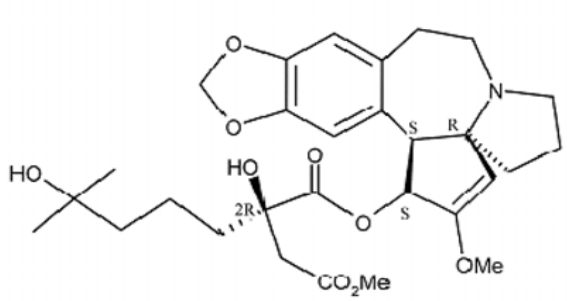
Management of Patients with CML After Failure of Two Prior TKIs
Patients with chronic myelogenous leukemia who are relapsed, refractory, or intolerant of at least two of the approved tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, and bosutinib) have limited treatment options and a poor prognosis. The only curative treatment available for CML is allogeneic hematopoietic stem cell transplantation (HSCT). However, not all patients have available donors and due to comorbidities, may not be able to tolerate HSCT.

Since 2003, the FDA has approved four oral tyrosine kinase inhibitors (TKIs) for the treatment of Philadelphia chromosome positive chronic myelogenous leukemia. For the approved CML TKI drugs, FDA has required 24 months of median follow-up data in order to grant regular approval (or to convert from accelerated approval to regular approval). Lesser amounts of follow-up data have resulted in the FDA granting accelerated approval. The trials have all been single-arm for the initial accelerated approvals. MCyR has been accepted as the efficacy endpoint for patients with Chronic Phase CML. Either MaHR or CHR have been accepted as efficacy endpoints for Accelerated Phase and Blast Phase CML in previous approvals. There are no currently approved agents for treatment of CML after failure of two TKIs.

3. CMC/Device

The Office of New Drug Quality Assessment CMC review was conducted by Debasis Ghosh, Ph.D., M.Pharm. The overall recommendation from CMC is approval.

The structural formula of omacetaxine mepesuccinate is presented below:



Molecular Formula: C29H39NO9 **Molecular Weight**: 545.6 g/mol

Drug substance stability is referenced to DMF 20542. The drug substance is sensitive to light. Based on the stability data, all stability testing results for the primary registration lots of omacetaxine mepesuccinate drug substance remained within the current specification criteria through 36 months storage at both the 5°C and 25°C/60%RH conditions and through 6 months storage at the 40°C/75%RH condition.

The proposed retest period (b) (4) when stored at 5°C or 25°C/60%RH and protected from light is acceptable. Based on the submission, for omacetaxine mepesuccinate for injection, the shelf-life of 18 months when stored at 20°C to 25°C (68°F to 77°F) excursions permitted to 15°C to 30°C (59°F to 86°F) and protected from light can be granted.

An 'Overall Acceptable' site recommendation from the Office of Compliance has been made on 04-Sep-2012.

The CMC review executive summary provides the following:

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An 'Overall Acceptable' site recommendation from the Office of Compliance has been made. From the CMC perspective, this NDA is recommended for approval pending the satisfactory resolution of the labeling issues.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

The product microbiology reviewer, Erika Pfeiler, recommended omacetaxine for approval on the basis of product quality microbiology.

Elsbeth Chikhale, PhD (CMC Reviewer) reviewed the biowaiver request. Her findings are below.

The proposed drug product is a lyophilized powder for injection containing omacetaxine mepesuccinate as the active ingredient and mannitol as the inactive ingredient. The drug product is a lyophilized powder that is reconstituted with 1.0 mL 0.9% sodium chloride immediately prior to subcutaneous injection. The clinical formulation and commercial formulation are different as shown in Table 1 below. The clinical formulation and commercial formulation should be linked by a BE study or a Biowaiver request should be submitted. The original NDA did not contain a BE study or a Biowaiver request. In response to an information request (IR) dated 5/10/12, a Biowaiver request was submitted in an amendment to the NDA dated 5/21/12. This review is focused on the evaluation of the Biowaiver request.

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

4. Nonclinical Pharmacology/Toxicology

The following material was excerpted from the executive summary of M. Stacey Ricci, M.Eng., Sc.D.

"The Pharmacology/Toxicology data to support NDA 22374 for omacetaxine was reviewed by Dr. Timothy Kropp. From the Pharmacology and Toxicology perspective, the review team recommended approval for NDA 22374 but requested post-approval that the battery of genotoxicity studies be completed according to ICH S2. Other review disciplines identified deficiencies in the NDA and the NDA was not approved. On March 30, 2012, Cephalon, Inc. submitted a new NDA for omacetaxine. The pharmacology and toxicology studies included in NDA 22374 were also included in NDA 203585. NDA 203585 contained additional studies, including new genotoxicity studies that were not reviewed previously. This review is an Addendum to the Pharmacology and Toxicology NDA review that was completed for NDA 22374 and archived in DARRTS on March 5, 2010 by Dr. Kropp.

Studies submitted to NDA 203585 that were not submitted previously are:

Genetic Toxicology
PTX-030 Bacterial Mutagenicity AMES Assay
PTX-031 *In vivo* mouse micronucleus assay

Pharmacology
CS-2011-
019-US Profiling of CEP-41443 in a Kinase Panel (b) (4)

- Omacetaxine did not induce genetic mutations in the Ames assay.
- Omacetaxine did not induce genetic damage using an *in vivo* mouse micronucleus assay.
- Omacetaxine did not inhibit kinase activity under conditions used to test 71 kinases using an *in vitro* screening assay.
- 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. *In vitro*, omacetaxine reduced protein levels of the Bcr-Abl oncoprotein (wild type or the T315I mutant) and Mcl- 1, an anti-apoptotic Bcl-2 family member. In a mouse model of Bcr-Abl-induced CML, omacetaxine had activity against both wild-type Bcr-Abl or Bcr-Abl with the T315I kinase domain mutation.

Recommendation
We recommend approval of omacetaxine from the pharmacology and toxicology standpoint for the proposed indication.

5. Clinical Pharmacology/Biopharmaceutics

The original NDA (22-374) clinical pharmacology review was conducted by Dr. Pengfei Song. The reader is referred to the 03/25/10 Clinical Pharmacology review by Dr. Song.
The Clinical Pharmacology review for the current NDA was conducted by Joseph Grillo, Pharm. D. The following text is excerpted from Dr. Grillo's review:

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

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

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

Study CGX-635-205 is the only applicant-sponsored clinical pharmacology study to evaluate single- and multiple-dose PK as well as QTc interval prolongation of omacetaxine in 21 cancer patients. Peak concentrations of omacetaxine are reached 0.5-1 hour after SC injection of Omacetaxine. Omacetaxine has a mean ±SD steady-state volume of distribution of approximately 141±93.4 L following SC administration for 11 days.

The plasma protein binding of omacetaxine is less than or equal to 50%. Omacetaxine is primarily hydrolyzed to the inactive 4′-DMHHT metabolite via plasma esterases with little hepatic microsomal oxidative and/or esterase-mediated metabolism *in vitro.* The major elimination route of omacetaxine is unknown, but will be evaluated post-market. The

mean percentage of omacetaxine excreted unchanged in the urine is less than 15%. The mean half-life of omacetaxine and 4′-DMHHT following SC administration is approximately 6 hours and 16 hrs, respectively. The plasma AUC of DMHHT is approximately 13% of omacetaxine AUC. Compared to a single dose, the plasma exposure to omacetaxine at steady state increased 90% following SC injection BID. Interpatient variability in omacetaxine AUC was 70%.

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

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

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

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

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

There were no post-marketing commitments recommended by OCP.

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

The Pharmacometrics review was conducted by Jee Eun Lee, Ph.D.
The following is excerpted from the question-based review by Dr. Lee.
Is body surface area-based dosing appropriate for omacetaxine?
No. The reviewer's analysis found that clearance of omacetaxine was not correlated with

BSA and thus BSA-based dosing might fail to achieve effective concentrations in patients with lower body size, such as women. An effect of gender on efficacy was observed from a subgroup analysis of the pivotal trials. For CML-CP patients, the primary endpoint, MCyR rates was 22% in men and 16% in women. The secondary endpoint, MaHR rate was 71% in men and 66% in women. For CML-AP patients, the primary endpoint, MaHR rate was 32% in mean and 19% in women. The effect of gender on exposure is noteworthy but it is rather attributable to lower dosing in female patients who have lower body surface area (BSA) when clearance was not correlated with BSA.

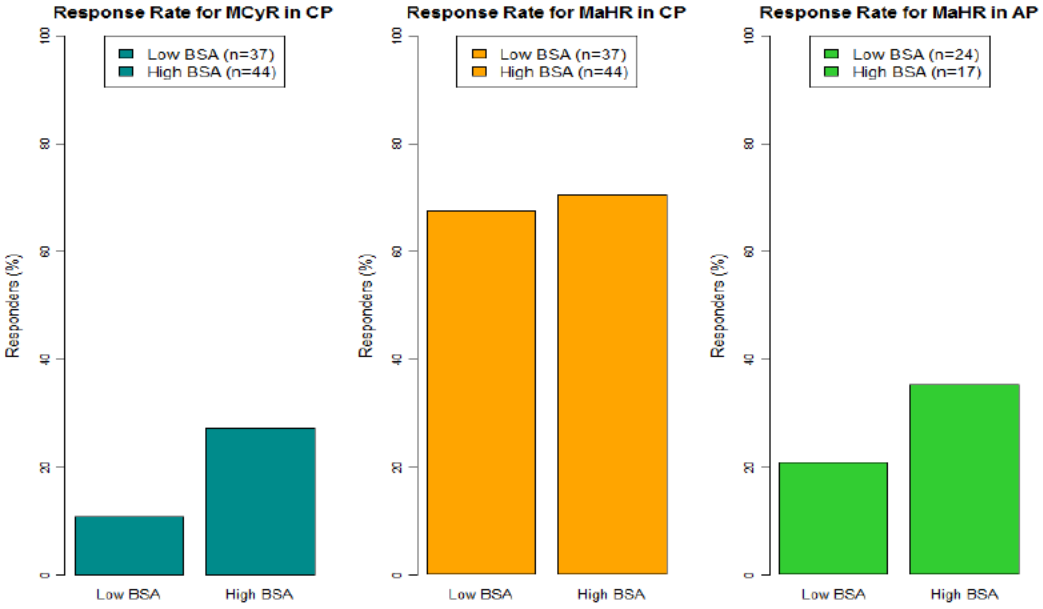
Are the proposed labeling statements supported by the sponsor's modeling and simulation?

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

Effect of BSA on Efficacy Results from Analysis 300

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

Response Rates for MCyR, MaHR, by BSA



Due to the small sample size, a definitive conclusion is not feasible. Nonetheless, the

increasing trend in all three endpoints is likely to support the need of increasing dose in patients with lower BSA and the potential of an optimal dose as fixed dosing regimen.

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

CDTL Comment: The Clinical Pharmacology team recommended that information regarding lower efficacy in women be included in labeling. The clinical team did not agree with this plan because the patient numbers were too small to draw conclusions. The clinical team did however agree that a PMC be given to further explore this issue.

6. Clinical/Statistical- Efficacy

The clinical review was conducted by Firoozeh Alvandi, MD. The Statistical review was conducted by Chia Wen Ko, Ph.D. Excerpts from this section were taken from their reviews. I concur with the clinical and statistical reviewer's recommended regulatory action.

Overall Recommended Regulatory Action: Accelerated approval 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).

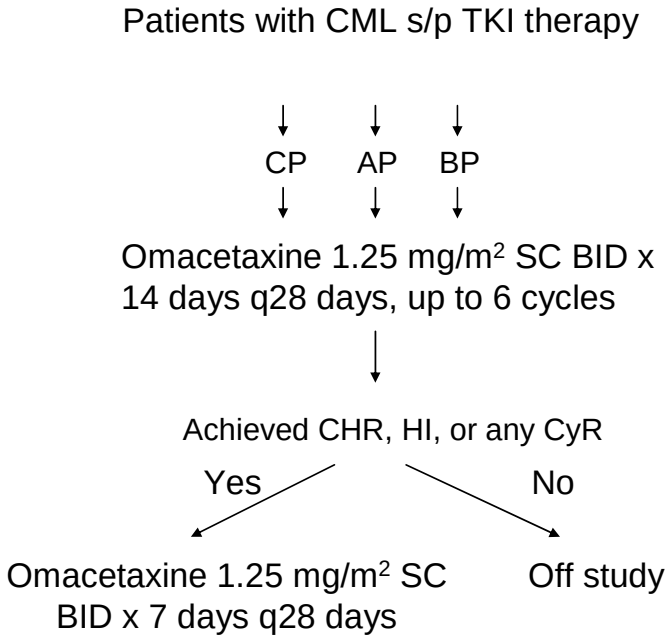
This recommendation is based upon inadequate median follow up duration for patients in the trial to support regular approval. The Applicant did not provide the requisite 24 months of follow-up data that FDA expects for regular approval. The submission contained a median of 19.5 (range 14.4-23.1) and 11.5 (range 6.8-16) months of follow up data for the primary endpoints for CML-CP and CML-AP population, respectively.

The indication was amended to reflect the third-line indication.

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 CML 4.2/4.3 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 primary efficacy endpoint for chronic phase CML was major cytogenetic response (MCyR), which included complete and partial cytogenetic responses. The primary efficacy

endpoint for accelerated phase CML was major hematologic response (MaHR), which included complete hematologic response (CHR) and no evidence of leukemia (NEL). The trial design of CML-202 and CML-203 is pictured below:



Sample size calculation is not applicable to supplemental analysis CML-300, because the study size was not driven by any statistical considerations. For response rates, summary statistics include numbers and percentages of patients with response and the exact one-sided lower 95% confidence limit were reported. For time-to-event variables, statistics reported include number and percentage of censored, median and the 95% confidence interval for the median using the Kaplan-Meier product-limit estimate.

The efficacy results differed from those provided by the Applicant in the following ways:

1. Inspection by the Division of Scientific Investigation (DSI) was found to be unreliable at sites 22 and 30 because of critical findings of deviations from regulations. *Data from sites 22 and 30 will not be used in this review.*
2. Two patients with CML-CP had MCyR (the main efficacy endpoint for this population) at trial entry. *Efficacy data for these two patients will not be counted in the analyses.*
3. Nine patients with CML-AP were in CHR (the main efficacy endpoint for this population) at baseline. *Efficacy data for these two patients will not be counted in the analyses.*
4. Blast phase patients were not counted in the analyses.

The FDA efficacy analysis population includes patients with chronic or accelerated phase CML, who received at least 2 prior TKIs, were not in best response at baseline, and were not enrolled at the sites that DSI found unreliable. The table below shows the patient demographic criteria for FDA efficacy analysis population. The FDA efficacy analysis population included a total of 111 patients, 76 patients in the chronic phase and 35 patients in the accelerated

disease phase. The demographic analyses were reproduced for this CDTL review because neither the statistical review nor the clinical reviews provided these analyses based upon the 111 patients that were selected for the final efficacy analysis.

FDA Efficacy Analysis Population Demographic and Baseline Disease Characteristics

Variable	Chronic Phase (n=76)	Accelerated Phase (n=35)	Total (n=111)
Age (years)			
Median (Minimum, Maximum)	59 (26, 83)	63	60
% 65 years or older	30	46	35
Gender			
% Male	62	57	60
Region n(%)			
USA	26 (34)	17 (49)	43 (39)
France	26 (34)	6 (17)	32 (29)
Poland	5 (7)	3 (9)	8 (7)
Canada	5 (7)	1 (3)	6 (5)
Hungary	3 (4)	3 (9)	6 (5)
Italy	4 (5)	1 (3)	5 (5)
Germany	3 (4)	1 (3)	4 (4)
Great Britain	1 (1)	2 (6)	3 (3)
India	1 (1)	1 (3)	2 (2)
Singapore	2 (3)	0	2 (2)
Gender n(%)			
Female	29 (38)	15 (43)	44 (40)
Male	47 (62)	20 (57)	67 (60)
Race n(%)			
White	61 (80)	24 (69)	85 (77)
Black or AA	4 (5)	8 (23)	12 (11)
Other	5 (7)	1 (3)	6 (5)
Asian	3 (4)	1 (3)	4 (4)
Hispanic	3 (4)	1 (3)	4 (4)
Age n(%)			
Median	59	63	60
Min	26	23	23
Max	83	83	83
# over 65	23 (30)	16 (46)	39 (35)
ECOG Status n(%)			
0	51 (67)	10 (29)	61 (55)

1	23 (30)	18 (51)	41 (37)
2	2 (3)	6 (17)	8 (7)
3	0	1 (3)	1 (1)
Median Time from CML Diagnosis (min, max)	73.4 (7.9, 234)	102.3 (23.6, 285.6)	82.5 (7.9, 285.6)
Baseline Disease Status of CHR n(%)	21 (28)	3 (9)	24 (22)
Prior TKIs Failed n(%)			
Imatinib and Dasatinib	29 (38)	10 (29)	39 (35)
Imatinib and Nilotinib	11 (14)	3 (9)	14 (13)
Imatinib, Dasatinib, and Nilotinib	36 (47)	22 (29)	58 (52)
TKI Resistance Intolerance Groups n(%)			
Resistance to ≥2 Approved TKIs	65 (86)	30 (86)	95 (86)
Intolerance to 1, Resistance to 1	4 (5)	2 (6)	6 (5)
Intolerance to ≥2 Approved TKIs	7 (9)	3 (9)	10 (9)

Source: Table generated by CDTL from Applicant Data Table ADSL

Disposition data analyses were conducted by Dr. Ko (Statistician) and were not repeated by for the CDTL memo because the datasets provided dates in SAS format, limiting the ability to repeat the analyses. The Applicant did not provide an adequate define.pdf file with the application. The define.pdf file did not list or describe all of the variables that were included in the datasets, so it was difficult to identify the variables of interest to be able to repeat the Sponsor's analysis. The statistician was provided with SAS programs to assist in replicating the analyses. These are not useful in JMP, the software program used by the clinical reviewers.

The following analyses (from Dr. Ko's review) are based upon a population of 119 patients (78 in Chronic Phase, 41 in Accelerated Phase). This population includes patients who were enrolled to the trial in best response. The overall baseline criteria analysis did not differ significantly when the patients in baseline best response were removed. Only the primary efficacy analyses were affected. Those analyses are presented here with the patients at best response at baseline removed.

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

cutoff date) was 20.0 months with a range of 2.6 to 47.7 months in the CP patients, and was 15.7 months with a range of 1.3 to 43.5 months in the AP patients.

Disposition of Patients (FDA Efficacy Analysis Population)

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

*Source: Dr. Ko's review

For the FDA Efficacy Analysis Population, the efficacy results for labeling purposes are:

Efficacy Results Evaluated by DMC for Chronic Phase-CML

	Patients (N=76)
Primary Response - MCyR	
Total with MCyR, n (%)	14 (18.4)
95% confidence interval	(10.5% - 29.0%)
Cytogenetic Response, n (%)	
Confirmed complete	6 (7.9)
Confirmed partial	3 (3.9)

The mean time to MCyR onset in the 14 patients was 3.5 months. The median duration of MCyR for the 14 patients was 12.5 months (Kaplan-Meier estimate). The median follow-up time was 17.8 months for the patients in Chronic Phase.

Table 1 Efficacy Results Evaluated by DMC for Accelerated Phase-CML

	Patients (N=35)
Primary Response - MaHR	
Total with MaHR, n (%)	5 (14.3)
95% confidence interval	(4.5% - 30.3%)
CHR	4 (11.4)
NEL	1 (2.9)
Primary Response - MCyR	
Total with MCyR, n (%)	0

The mean time to response onset in the 5 patients was 2.3 months. The median duration of MaHR for the 5 patients was 4.7 months (Kaplan-Meier estimate). The median follow-up time for patients in Accelerated Phase was 9.6 months.

CDTL Comment: 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.

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Secondary Endpoints
The key secondary efficacy endpoints for Analysis CML-300 included progression free survival (PFS) and overall survival (OS), summarized in the **Error! Reference source not found.**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.

CDTL Comment: Time to event endpoints (b) (4) when obtained from single arm trials.

The results below for PFS and OS are excerpted from Dr. Ko's review.

Table 2 Progression Free Survival in Analysis 300

	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

CDTL Comment: Time to event endpoints are not evaluable in single-arm trials, therefore, no conclusions can be drawn. (b) (4)

Table 3 Overall Survival in Analysis 300

	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

CDTL Comment: Time to event endpoints are not evaluable in single-arm trials, therefore, no conclusions can be drawn (b) (4)

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

7. Safety

The evaluation of the safety of omacetaxine mepesuccinate in patients with CML is limited due to the single-arm design of the trials submitted for review. The Applicant submitted safety analyses that utilized investigator attribution. We found that this approach minimized the incidence of most adverse reactions. The Agency has written guidance that this approach is not acceptable in single-arm trials.

Safety findings are summarized here from Dr. Firoozeh Alvandi's review.
Omacetaxine has a positive risk:benefit assessment for patients with CML-CP or CMLAP 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).

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. The data from patients with CML-CP and CML-AP in trials CML-202, CML-203, and CML-04.2/04.3 were used. 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. The Applicant's major safety analyses were reproduced using JMP software. 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.

The data from the studies using the SC route of administration of omacetaxine are presented and pooled, as summarized in the table 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.

Figure 1 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

The size of the safety population is adequate for the proposed indication. Prior approvals for CML have had similarly-sized safety population.

Safety Population Demographics

Figure 2 Chronic Phase CML Safety Population 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

Figure 3 Prior TKIs Received by Safety Population

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)

Exposure

Figure 4 Study Drug Exposure Safety Population

	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)

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).

Deaths

A total of 40 deaths were reported during the trial and follow-up period. Eight of the 40 occurred during the trial and within 30 days of the last dose of omacetaxine. Four deaths each occurred in the Chronic Phase and Accelerated Phase groups. There were two cases in each group of cerebral hemorrhage leading to death, one case each of Multiorgan failure and 'unknown causes', both in the Chronic Phase group. Bleeding is a serious clinical concern with omacetaxine. All of the patients with cerebral hemorrhage were thrombocytopenic, which increased their risk of bleeding.

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%).

Withdrawals

Treatment emergent adverse events leading to drug discontinuation were hematological (thrombocytopenia [11%], followed by pancytopenia [3%]).
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%).

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. The table 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.

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%).

Figure 5 Treatment Emergent Adverse Events in >10% of Patients with CP-CML

	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)

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%).

Figure 6 Treatment Emergent Adverse Events in >10% of Patients with AP-CML

	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)

Effects on QT

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.

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 a single 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.

Special Safety Studies

(b) (4)

(b) (4)

(b) (4). The Agency does not believe that chemotherapeutic agents should be mixed at home by the patient.

8. Advisory Committee Meeting

No Advisory Committee meeting was held for this application. As previously discussed, the application was brought to advisory committee in 2010 for the initial NDA submission by Chemgenex.

9. Pediatrics

In accordance with the Pediatric Rule 21 CRF 314.55(d), the requirement for submission of information on pediatric use does not apply to omacetaxine mepesuccinate as it has been granted orphan drug designation for use in patients with chronic myeloid leukemia, Orphan Designation 05-2182.

10. Other Relevant Regulatory Issues

Office of Scientific Investigations: Clinical site inspections were conducted by the Office of Scientific Investigations for the prior NDA submission (22374). OSI has determined (based upon EMA inspections) that data from European 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 followup 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."

There are no outstanding consults for this NDA.

11. Labeling

Proprietary name: Per DMEPA, the proposed proprietary name, Synribo, is acceptable from both a promotional and safety perspective.

The nearly final labeling was reviewed by the DMEPA reviewer, Gina McNight-Smith. Her recommendations were implemented in the final labeling prior to submission to Teva.

Physician labeling was sent back to the Applicant on Monday, October 1, 2012. We requested response from them by close of business, October 4th. On October 2, 2012, they requested that a Tcon be scheduled to discuss some of the labeling changes made by the Agency. This Tcon will be held on October 5th.

Major issues with the Applicant's labeling were as follows:

- The efficacy data displayed included patients who were enrolled at sites 22 and 30 as well as those who entered the trial in their best response (MaHR or MCyR), which artificially inflates the response rates for omacetaxine.

(b) (4)

- The labeling included a description of omacetaxine as a protein synthesis inhibitor. Omacetaxine does not belong to a pharmacologic class, so this information was removed at the recommendation of the Pharmacology Toxicology review team.
- The review team concluded that no Medication Guide or REMS was required for this NDA.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
  Accelerated approval

- 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.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
No REMS are recommended.

- Recommendation for other Postmarketing Requirements and Commitments

Post-Marketing Requirements: Agreed upon by FDA and Applicant

1. PMR Description:	Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of CGX-635-CML-300 with 24 months of minimum follow-up data for each patient. If 24 months of follow-up is not possible for certain patients, justification should be provided.	
PMR Schedule Milestones:	Final Protocol Submission:	n/a
	Study / Trial Completion:	03/2012
	Final Report Submission:	04/2013
2. PMR Description:	Conduct a mass balance trial in humans to determine the disposition and elimination pathways as well as to characterize the major metabolites of omacetaxine following subcutaneous injection. Depending on the results, hepatic and/or renal impairment trials may be required.	
PMR/PMC Schedule Milestones:	Preliminary Protocol Submission	07/2012
	Final Protocol Submission:	10/2012
	Study/Trial Completion:	06/2015
	Final Report Submission:	12/2015
3. PMR Description:	Conduct a Phase 1/2 single arm clinical trial to investigate the pharmacokinetics, safety, and preliminary efficacy of omacetaxine following fixed dose administration in patients with chronic phase (CP) of chronic myeloid leukemia (CML) or acute phase (AP) of chronic myeloid leukemia (CML) who have failed TKI therapy. In Cycle 1, evaluate the PK and safety of omacetaxine following fixed dose administration. Continue treatment if tolerated using a fixed dose as long as patients are clinically benefiting from therapy.	

	Include in the action letter, but not in the PMR text itself: Sponsor should submit labeling to incorporate the results.	
PMR Schedule Milestones:	Preliminary Protocol Submission	12/2012
	Final Protocol Submission:	03/2013
	Trial Completion:	02/2016
	Final Report Submission:	06/2016

PMR #1 is required to convert the accelerated approval to regular approval. The FDA requires 24 months of follow-up data to be considered for regular approval in the CML indication. This trial is required under Subpart H.

PMR #2 Is requested by Clinical Pharmacology to evaluate the need for organ impairment trials, which have not yet been conducted. This trial is required under FDAAA.

PMR #3 is also requested by Clinical Pharmacology to evaluate whether fixed dosing may be a better alternative to BSA based dosing, which was utilized in the clinical trials and resulted in a lower exposure in female patients with lower BSAs and may have resulted in lower efficacy in women in the two phase 2 trials supporting the NDA. This trial is required under FDAAA.

References

1. (American Cancer Society.: Cancer Facts and Figures 2012. Atlanta, Ga: American Cancer Society, 2012. Accessed July 31, 2012.)

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VIRGINIA E KWITKOWSKI
10/02/2012