

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203585Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Synribo (omacetaxine mepesuccinate)

Date: October 9, 2012

To: File for NDA 203585

From: John K. Leighton, PhD, DABT

Acting Director, Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

I have examined pharmacology/toxicology supporting reviews of Drs Kropp and Ricci and secondary memoranda and labeling provided by Dr. Saber. I concur with Dr. Saber's conclusion that Synribo may be approved and that no additional nonclinical studies are needed for the proposed indication.

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/s/

JOHN K LEIGHTON
10/09/2012

MEMORANDUM

Date: October 7, 2012
From: Haleh Saber, Ph.D.
Pharmacology/Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
NDA: 203585;
Also see the Supervisory Pharmacologist memorandum under NDA 22374
Drug: SYNRIPO, omacetaxine mepesuccinate
Indication: Treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors
Applicant: Cephalon Inc. (Teva Pharmaceuticals, Ltd)

Background

The mechanism of action of omacetaxine is not fully understood. Omacetaxine exerts its anticancer activity at least in part by interfering with protein elongation and inducing apoptosis. The marketing application for omacetaxine was originally submitted in 2009, under NDA # 22374. The pharmacology/toxicology team recommended approval while recognizing that the battery of genotoxicity studies was incomplete and studies needed to be conducted post-approval or as soon as feasible. Subsequently, a complete response (CR) letter was issued in 2010. The nonclinical comment for completing the battery of genetic toxicology studies was included in the CR letter among deficiencies from other disciplines.

In the current submission, the Applicant has submitted results of two genetic toxicology studies in addition to other nonclinical studies. The studies were reviewed by Dr. Stacey Ricci under NDA 203585. A previous genetic toxicology study was reviewed by Dr. Kropp under NDA 22374. The results indicate that omacetaxine was positive in the *in vitro* chromosome aberration assay and negative in the Ames test and in *in vivo* micronucleus assay.

Reviews of NDAs 22374 and 203585 will be used to revise the nonclinical sections of the label. Results of nonclinical studies are summarized in Dr. Kropp and Dr. Ricci's review and in the Supervisory Pharmacologist memorandum of March 5, 2010. Of note, since the systemic exposure (AUC) data are not available for the embryofetal reproductive toxicology study, the dose conversions will be used in the label for animal:human comparisons under Section 8.1.

Due to the lack of adequate understanding of the mechanism of action of SYNRIPO, a pharmacologic class has not been assigned to this drug.

Recommendation: I concur with Dr. Ricci that from a nonclinical perspective, SYNRIPO may be approved for the proposed indication. No additional nonclinical studies are needed to support approval of SYNRIPO for the proposed indication.

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/s/

HALEH SABER
10/07/2012

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 203585
Supporting document/s: 1
Applicant's letter date: March 30, 2012
CDER stamp date: March 30, 2012
Product: Omacetaxine mepesuccinate
Indication: Adult patients with chronic or accelerated phase
CML with resistance or intolerance to prior
tyrosine kinase
Applicant: Cephalon, Inc. (a wholly owned subsidiary of
Teva Pharmaceuticals, Ltd.)
Review Division: Hematology and Oncology Toxicology on behalf
of the Division of Hematology Products
Reviewer: M. Stacey Ricci, M.Eng., Sc.D.
Supervisor/Team Leader: Haleh Saber, Ph.D.
Division Director: John Leighton, Ph.D.
Project Manager: Theresa Ferrara, M.P.H.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203585 are owned by Cephalon, Inc. or are data for which Cephalon, Inc. has obtained a written right of reference.

Any information or data necessary for approval of NDA 203585 that Cephalon, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203585.

Executive Summary

Introduction

An NDA for omacetaxine mepusuccinate (hereafter referred to as 'omacetaxine') was first submitted to FDA on Sept. 8, 2009. 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.

Recommendation

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

Background

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

Genetic Toxicology	
PTX-030	Bacterial Mutagenicity AMES Assay
PTX-031	<i>In vivo</i> mouse micronucleus assay
Pharmacology	
CS-2011-019-US	Profiling of CEP-41443 in a Kinase Panel (b) (4)
Pharmacokinetics	
PTX-029	<i>In vitro</i> assessment of protein binding for homoharringtonine (HHT) in human plasma using the ultrafiltration method
PTX-028	P-glycoprotein inhibition potential of homomharringtonine (HHT) and 4-demethyleated homoharringtonine
CLN003	<i>In vitro</i> assessment of protein binding for homoharringtonine (HHT) in human plasma
PTX-027	<i>In vitro</i> evaluation of omacetaxine as an inducer of cytochrome p450 expression in cultured human hepatocytes

The Genetic Toxicology and Pharmacology studies listed above are reviewed below; the Pharmacokinetics studies were not reviewed. Peer-reviewed literature submitted in the NDA that are pertinent to the description of omacetaxine pharmacology proposed for the Package Insert are also reviewed below.

Nonclinical Findings

- 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.

Summary of all genotoxicity results for studies submitted in NDA 203585

Test	Study Report Number	Result
Ames Assay	PTX-004*	Negative; test was not adequate for hazard identification purposes because dosing used was insufficiently low.
Ames Assay	PTX-030	Negative
<i>In vitro</i> Chromosome Aberration Analysis in CHO cells	PTX-080*	Positive
<i>In vivo</i> Mouse Micronucleus Assay	PTX-031	Negative

*Study reviewed by Dr. Timothy Kropp for NDA 22374.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Mutagenicity Test – Ames Assay

Study no.: PTX-030
 Study report location: NDA 203585 Section 4.2.3.3.1
 Conducting laboratory and location: (b) (4)

Date of study initiation: November 19, 2010
 GLP compliance: Yes; signed statement provided
 QA statement: Yes; signed statement provided
 Drug, lot #, and % purity: Omacetaxine Mepesuccinate (powder), Lot #12252,

Key Study Findings

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.

Methods (plate incorporation assay)

Strains: *Salmonella typhimurium* strains:
TA97a, TA98, TA100, and TA1535
E. coli strain: WP2-uvrA⁻

Concentrations in definitive study: With S9:
5.0, 1.582, 0.501, 0.159, 0.050 mg/plate

Without S9:
1.582, 0.501, 0.159, 0.050, 0.016 mg/plate

Basis of concentration selection: The test article was diluted in 100% DMSO. A dose-range finding study determined that doses of 5.0 and 1.582 mg/plate with metabolic activation induced substantial toxicity in strain TA100 and resulted in no colony formation and an absent micro-colony lawn.

Negative control: DMSO

Positive control: With S9:
2-aminoanthracene (10.0 µg/plate) for all strains except TA1535 which used a concentration of 1.6 µg/plate

Without S9:
TA97a: ICR-191 Acridine (1.0 µg/plate)
TA98: 2-nitrofluorene (10.0 µg/plate)
TA1535/TA100: sodium azide (1.5 µg/plate)

Formulation/Vehicle: DMSO

Incubation & sampling time: 3 plates per treatment
Plates were incubated 48-72 hours at 37°C.
Plates were counted using an automatic image analysis system.
Negative control and test article treated plates were also examined for the presence of a bacterial lawn.

Study Validity

Bacterial strains used conform to ICH S2A recommendations. Positive and negative controls produced expected responses (see results tabulated below). Dose selection for the plate incorporation method was adequate based upon use of the limit dose (i.e., 5000 µg/plate).

Results

The following results were compiled from data tabulated in the study report:

Average colony count per plate without S9:

Dose (mg/plate)	TA97a	TA98	TA100	TA1535	WP2-uvrA
5.000	89	33	106	19	16
1.582	102	32	112	11	19
0.501	103	31	111	14	14
0.158	107	29	112	11	19
0.050	106	29	112	18	18
-control	105	26	105	14	20
+control	1107	1176	988	444	96

Average colony count per plate with S9:

Dose (mg/plate)	TA97a	TA98	TA100	TA1535	WP2-uvrA
0.501	123	34	104	15	22
0.158	119	40	107	11	19
0.050	133	37	92	18	14
0.016	127	40	92	13	18
0.005	121	37	98	15	14
-control	124	30	83	12	15
+control	2009	1254	820	181	252

Historic reversion rates for the (b) (4) were provided and the background results provided fall within the ranges for the omacetaxine treatments and negative controls.

Conclusions

The Ames assay results indicate that omacetaxine is not a bacterial mutagen under the conditions tested.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)**Study title: In Vivo Mouse Micronucleus Assay**

Study no: PTX 031
 Study report location: NDA 203585 Section 4.2.3.3.2.1
 Conducting laboratory and location: (b) (4)

Date of study initiation: January 6, 2011
 GLP compliance: Yes, signed statement provided
 QA statement: Yes, signed statement provided
 Drug, lot #, and % purity: Omacetaxine mepesuccinate (powder),
 Lot #12252,

Key Study Findings

- Omacetaxine did not induce a dose-dependent increase in micronuclei formation in mouse erythrocytes derived from bone marrow.

Methods

Doses in definitive study:	0.095, 0.30, 0.95 mg/kg
Frequency of dosing:	Single administration
Route of administration:	Tail vein injection (IV)
Dose volume:	Dose volumes were not provided. Stock solution concentration = 0.3 mg/ml and lower doses were prepared by dilution immediately prior to use.
Formulation/Vehicle:	0.9% NaCl
Species/Strain:	<i>Mus musculus</i> /CD-1
Number/Sex/Group:	5/sex/group
Satellite groups:	None
Basis of dose selection:	A dose range study demonstrated some toxicity at the high dose of 3.0 mg/kg. The next highest 3 doses were chosen for the definitive study.
Negative control:	0.9% NaCl
Positive control:	75 mg/kg cyclophosphamide

Study Validity

- A dose-range finding study was conducted in which 3 males per group received a single IV administration of 0.030, 0.095, 0.30, 0.95, 3.0 mg/kg followed by bone marrow collection 24h post-dosing. In the high dose group, 1/3 males appeared lethargic and had a spiked coat within one hour-post dose. The two other males in this group also exhibited a spiked coat four hours post-dosing. The next morning, 2/3 males “still showed some signs of toxicity” but were responsive to stimuli. All other mice appeared bright, active and responding to stimuli throughout. The sponsor chose to use 0.95 mg/kg as the maximum dose for the definitive study based on the toxicities observed in the 3.0 mg/kg group. ICH S2(R1) and Redbook 2000¹ recommends that the highest dose used produce signs of toxicity but not be expected to produce lethality. Based on this recommendation, the maximum dose used in the definitive study is low since there was no evidence of toxicity observed in the group that received 0.95 mg/kg.
- Results from an acute toxicity study using CDF₁ mice (Study Report PTX-013 conducted in 1981) identified single IV dose levels that were not lethal, but were higher than the dose levels used in the *in vivo* micronucleus study (Study PTX-013 used doses ranging from 0.80 to 10

¹<http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/Redbook/ucm078338.htm>

mg/kg). Clinical signs of toxicity (ruffling of the coat) were observed at 4.31 mg/kg or higher in both sexes, and lethargy at 6.56 mg/kg in females and at 10 mg/kg in males. No deaths were observed in groups receiving the 2.13 mg/kg or lower dose.

- However, results from the definitive study demonstrated a small decrease in numbers of immature erythrocytes in samples from the highest dose tested, indicating that systemic exposure to omacetaxine was sufficient to elicit toxicity.
- Bone marrow was harvested 24 and 48 hours after dosing. Immediately after harvest, three blood smears per mouse were prepared. Slides were stained and scored visually. Two thousand polychromatic erythrocytes (PCE) were scored for the presence of micronuclei. The proportion of PCE to 500 mature erythrocytes was determined as a measure of toxicity. The preparation and analysis of cells is acceptable.
- The positive control used produced significant levels of micronuclei formation (~30 fold and ~50 fold in females and males, respectively). The number of micronuclei in the negative controls is within the historical ranges for the conducting laboratory.

Results (Data tables shown were copied from the study report)

There was no dose-dependent increase in micronuclei formation in either males or females. Curiously, the amount of micronuclei increased at the low dose of omacetaxine but the increase was not statistically significant according to the ANOVA test used. The relevance of this finding is unknown.

TABLE 4
AVERAGE MICRONUCLEATED POLYCHROMATIC ERYTHROCYTES RATES
PER 1000 POLYCHROMATIC ERYTHROCYTES*

TREATMENT	FEMALES		MALES	
	24 HR INDUCTION	48 HR INDUCTION	24 HR INDUCTION	48 HR INDUCTION
0.950 mg/kg	0.8	0.6	1.4	1.8
0.300 mg/kg	1.6	0.7	1.3	2.4
0.095 mg/kg	2.7	2.2	3.2	2.2
Negative Control	1.4	1.2	0.9	1.5
Cyclophosphamide 75 mg/kg	35.3*	Not Tested	50.6*	Not Tested

*Micronucleus induction significantly greater than in either negative control (One-way ANOVA; $p < 0.001$)

As shown in the table below, the high dose caused a small but statistically

significant decrease in the ratio of immature to mature (PCE:RBC²) erythrocytes in males after 24h and in females after 24h and 48h. A small *increase* was observed in males treated with the mid dose (0.30 mg/kg) after 24h, but not 48h. The relevance of this increase is unknown. The positive control did not demonstrate a change in the ratio of PCE:RBC.

TABLE 5 – EFFECTS OF TREATMENT ON ERYTHROPOIESIS

TREATMENT	FEMALES		MALES	
	24 HR INDUCTION	48 HR INDUCTION	24 HR INDUCTION	48 HR INDUCTION
0.950 mg/kg	0.9*	0.5*	0.6*	1.0
0.300 mg/kg	1.0	1.0	1.5*	1.0
0.095 mg/kg	1.0	1.0	1.0	1.0
Negative Control	1.0	1.0	1.1	1.0
Cyclophosphamide 75 mg/kg	1.0	Not Tested	1.0	Not Tested

*Erythropoietic ratio was found to be significantly different compared to the negative control.

Conclusions

While the maximum dose used did not cause clinically observable signs of toxicity, it did cause a decrease in the ratio of immature to mature erythrocytes when compared to the negative control. Therefore, the assay is considered adequate and demonstrated that omacetaxine did not induce a dose-dependent increase in micronuclei formation in mouse erythrocytes derived from bone marrow. However, the lowest dose used caused a non-statistically significant increase in micronuclei, but the relevance of this finding is unknown.

Study title: Profiling of CEP-41443 (omacetaxine mepusuccinate, Blind Code IN072511) in a Kinase Panel (b) (4)

Study no.: CS-2011-0190US

Study report location: NDA 203585 Section 4.2.1.1.1

Conducting laboratory and location: (b) (4)

Date of study initiation: August 5, 2011

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: Not provided

² Terminology used in the study report.

Key Study Findings

Cephalon contracted [REDACTED]^{(b) (4)} to conduct their Z'-LYTE® biochemical assay analysis to evaluate omacetaxine's ability to inhibit 71 kinases using a fluorescence-based, coupled-enzyme format.

- Omacetaxine was tested using a single concentration (1 microM). None of the kinases tested were inhibited by more than 25%, and most results were <10% inhibition.
- Study results are provided below:

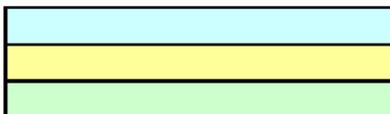
(b) (4) Kinase Profiling - Omacetaxine Mepesuccinate (CEP-41443)
Study SSBK8492_22628

Duplicate determinations at [ATP] = Km

>99% Inhibition

90-99% Inhibition

80-90% Inhibition



Kinase	Omacetaxine Mepesuccinate % Inhibition at 1 uM
ABL1	-6
ABL1 T315I	2
ACVR1B (ALK4)	11
AKT1 (PKB alpha)	4
AMPK A1/B1/G1	7
AURKA (Aurora A)	0
AURKB (Aurora B)	5
BTK	0
CDK1/cyclin B	4
CHEK1 (CHK1)	0
CLK1	0
CSNK1G2 (CK1 gamma 2)	5
CSNK2A1 (CK2 alpha 1)	-1
DAPK3 (ZIPK)	-1
DCAMKL2 (DCK2)	6
DYRK3	-5
EGFR (ErbB1)	8
EPHA2	2
EPHB1	-1
ERBB2 (HER2)	-3
FGFR1	15
FLT1 (VEGFR1)	6
FLT3	7
FLT4 (VEGFR3)	4
FRAP1 (mTOR)	3
GRK4	2
GSK3B (GSK3 beta)	-2
IGF1R	3
IKBKB (IKK beta)	0
INSR	1
IRAK4	-3
JAK3	6
KDR (VEGFR2)	1
KIT	11
LCK	5

MAP2K1 (MEK1)	22
MAP3K8 (COT)	11
MAP3K9 (MLK1)	4
MAP4K4 (HGK)	19
MAP4K5 (KHS1)	-6
MAPK1 (ERK2)	2
MAPK14 (p38 alpha)	7
MAPK8 (JNK1)	14
MAPKAPK2	-1
MARK1 (MARK)	-1
MET (cMet)	9
NEK1	-9
NEK7	-7
NTRK1 (TRKA)	20
PAK4	-19
PDGFRB (PDGFR beta)	0
PDK1 Direct	0
PHKG2	11
PIM1	6
PKN1 (PRK1)	7
PLK1	6
PRKACA (PKA)	-1
PRKCB1 (PKC beta I)	4
PRKCD (PKC delta)	-6
PRKCE (PKC epsilon)	-5
PRKG2 (PKG2)	-5
RET	1
ROCK1	-2
ROCK2	6
RPS6KA3 (RSK2)	0
RPS6KB1 (p70S6K)	9
SRC	0
STK22D (TSSK1)	2
SYK	5
TAOK2 (TAO1)	7
TEK (Tie2)	-3

Number of kinases (out of 71)

>99% Inhibition	0
90-99% Inhibition	0
80-90% Inhibition	0

S(90) 0.000

S(99) 0.000

Omacetaxine Pharmacology Published Literature Review

NDA 203585 contains four pharmacology studies, three of which were submitted previously under NDA 22374 and reviewed by Dr. Timothy Kropp. In addition, Cephalon provided literature references containing data that examined omacetaxine pharmacology. The three studies reviewed previously are:

Study Number	Study Title
TB-20081	Determination of the Relative Cytotoxicity of Homoharringtonine (HHT), 4'-DMHHT & Cephalotaxine (CTXOH) Against the Hematologic Cell Lines K-562, HL-60, Molt-4 and CCRF-CEM
TB-20084	Inhibitory Effects of Omacetaxine on Chronic Myeloid Leukemia (CML) and Bcr-Abl-Transduced Hematopoietic Stem Cells in Mice
TB-20085	Effects of Omacetaxine on the Expression of Bcl-2 family proteins in K562 Leukemia Cells

The pharmacology of omacetaxine (also known as homoharringtonine) has been investigated since the 1970s. Early work by Fresno *et al.* identified that *Cephalotaxus* alkaloids (harringtonin, homoharringtonine and isoharringtonine) inhibit the elongation phase of protein translation using ribosomes isolated from eukaryotic cells.³

A more recent study evaluated the crystal structure of homoharringtonine bound to the large ribosomal subunit from *H. marismortui* in an effort to understand its antibiotic properties.⁴ *Haloarcula marismortui* is a halophilic red Archaeon (from the Halobacteriaceae family) found in the Dead Sea, a high saline, low oxygen solubility, and high light intensity environment. Homoharringtonine competes with incoming aminoacyl-tRNAs for binding to the A-site cleft in the peptidyl transferase center. This paper cites other work that describes the ribosomal RNA sequences of archaea bacteria as being more closely related to eukaryotes than to eubacteria.

Study Report TB-20085 (conducted by ChemGenex) contains results from western blot analysis of protein lysates collected from Bcr-Abl positive-K562 cells that were treated with omacetaxine. Mcl-1 and Bim levels decreased in a dose-dependent manner, while Bax increased. Puma and Bcl-XI were not affected. The concomitant increase in pro-apoptotic Bax and decrease of Mcl-1 levels support the observation of increased apoptosis following omacetaxine treatment, while the significance of the decrease in Bim (a pro-apoptotic Bcl-2 family member) is unknown.

³ Fresno M, Jimenez A, Vazquez D. Inhibition of translation in eukaryotic systems by harringtonine. *Eur J Biochem.* 1977;72(2):323-330.

⁴ Gurel G, Blaha G, Moore PB, Steitz TA. U2504 determines the species specificity of the A-site cleft antibiotics: the structures of tiamulin, homoharringtonine, and bruceantin bound to the ribosome. *J Mol Biol.* 2009;389(1):146-156.

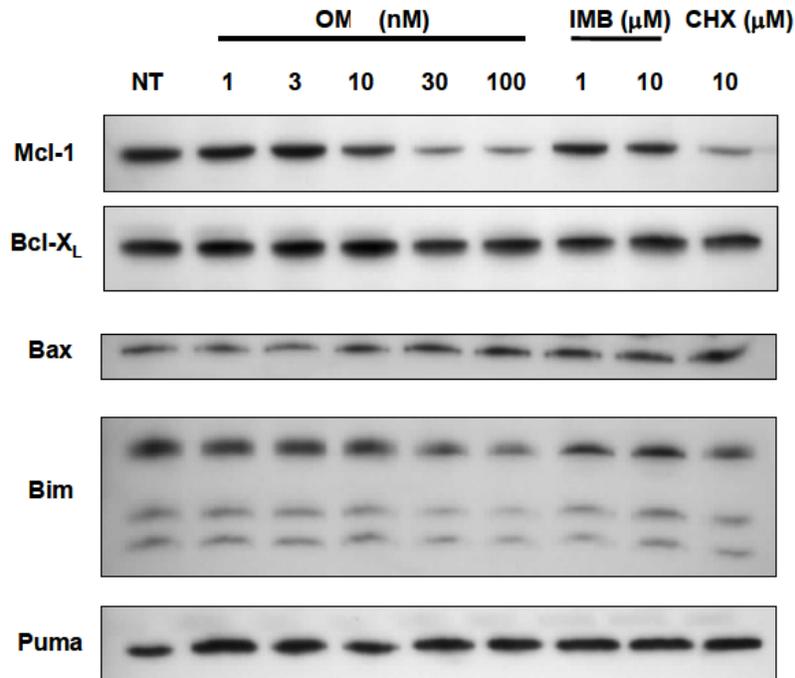
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Figure 2: Dose response analysis of the effect of omacetaxine on bcl-2 family protein expression

K562 cells were treated with omacetaxine (OM), imatinib (IM), cyclohexamide (CHX) or vehicle (not treated, NT) for 4 hours and protein lysates were prepared. 20ug of total protein was analyzed by PAGE and western blotting with antibodies specific for bcl-2 family proteins.

Data published by Chen et al.⁵ demonstrated that omacetaxine treatment of K562 cells resulted in a decrease of Bcr-Abl levels.

⁵ Chen R, Gandhi V, Plunkett W. A sequential blockade strategy for the design of combination therapies to overcome oncogene addiction in chronic myelogenous leukemia. *Cancer Res.* 2006;66(22):10959-10966

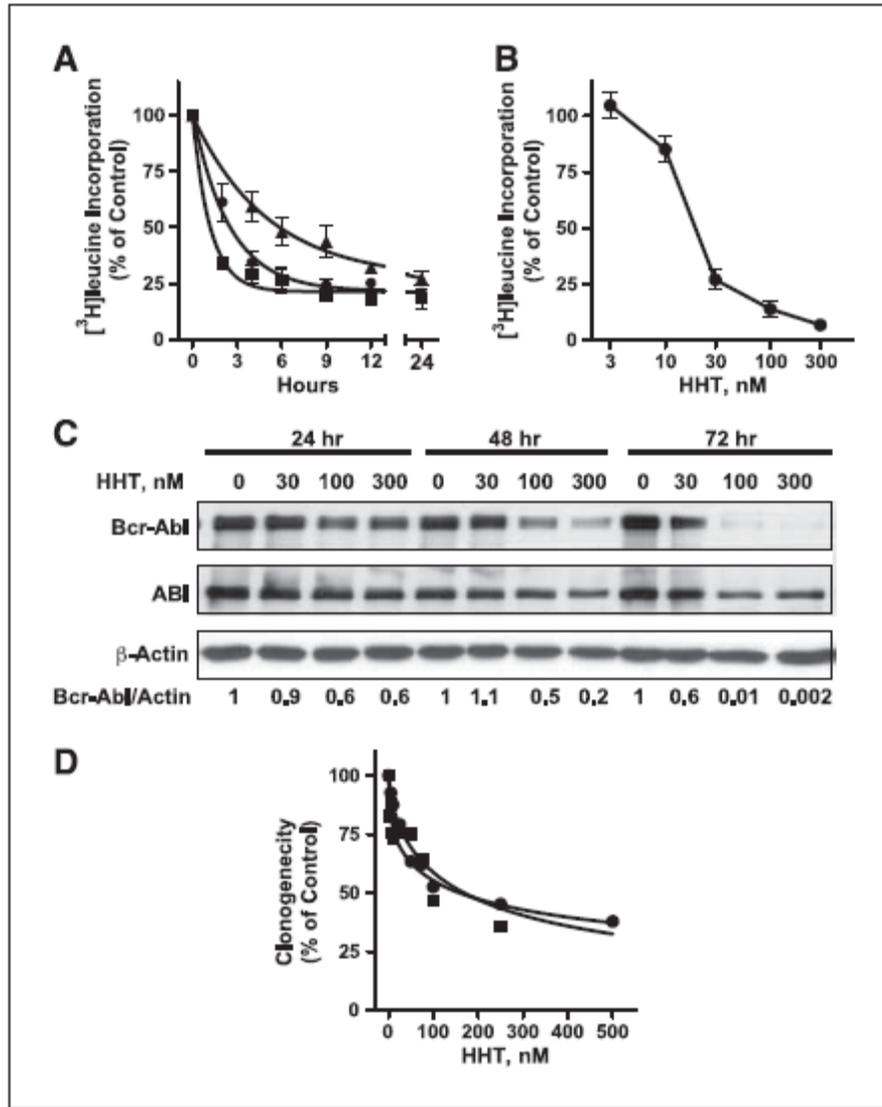


Figure 3. HHT inhibited protein synthesis and reduced the Bcr-Abl protein levels in K562 cells. **A**, time-dependent inhibition of protein synthesis by HHT. K562 cells were incubated with HHT [100 nmol/L (●) or 300 nmol/L (■)] or 2.5 μg/mL puromycin (▲) for the indicated time and then labeled with 1 μCi/mL [³H]leucine for 30 minutes. *Points*, mean percentage of protein synthesis compared with untreated controls of three independent experiments done in triplicate; *bars*, SE. **B**, concentration-dependent inhibition of protein synthesis by HHT. K562 cells were incubated with increasing concentrations of HHT for 24 hours and then pulse labeled with 1 μCi/mL [³H]leucine for 30 minutes. *Points*, protein synthesis expressed as the mean percentage of radioactivity compared with controls of triplicate data; *bars*, SD. **C**, Bcr-Abl protein decreased after incubation with HHT. K562 cells were incubated with 30, 100, or 300 nmol/L HHT or solvent for 24, 48, and 72 hours. Levels of Bcr-Abl and Abl protein were detected by immunoblot. Results were calculated as the ratio of the relative film density of Bcr-Abl and β-actin. β-Actin was used as a loading control. **D**, inhibition of clonogenicity by HHT in K562 cells after 24 hours (●) and 48 hours (■) of incubation. Data represent the percentage of control colonies. The IC₅₀ of inhibition of clonogenicity by HHT was 168 nmol/L for 24 hours and 158 nmol/L for 48 hours in experiments done in triplicate.

Data from a different laboratory illustrated that omacetaxine treatment of cell lines derived from primary mouse pre-B cells that had been retrovirally transduced with wt-Bcr-Abl or T315I-mutant Bcr-Abl resulted in decreased Bcr-Abl protein levels regardless of mutation status.⁶

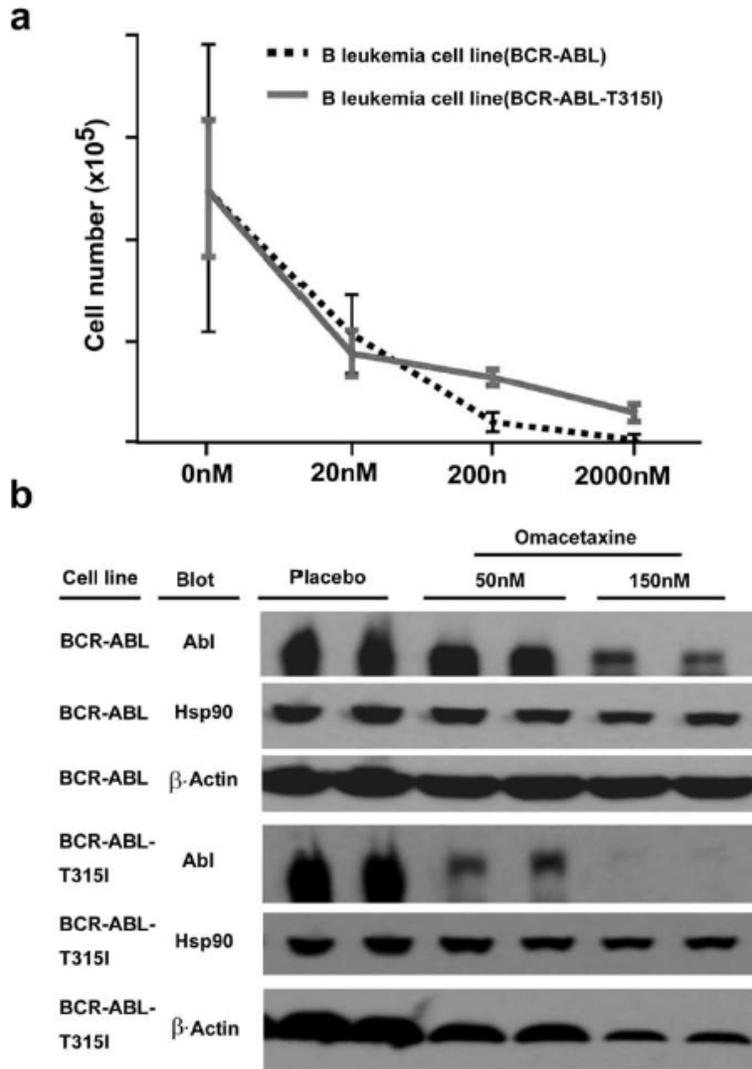


Figure 6. Omacetaxine inhibits B-ALL cells by suppressing BCR-ABL without affecting HSP90
a. Omacetaxine inhibited pre-B cells expressing BCR-ABL or BCR-ABL-T315I associated with drug concentration. The number of viable cells at the indicated drug concentrations was determined by trypan blue.
b. Omacetaxine inhibited the expression of ABL in pre-B cells expressing BCR-ABL or BCR-ABL-T315I. These pre-B cells were treated with omacetaxine (50 nM, 150 nM) for 48 hours. Protein lysates were analyzed by Western blotting using antibodies indicated.

⁶ Chen Y, Hu Y, Michaels S, Segal D, Brown D, Li S. Inhibitory effects of omacetaxine on leukemic stem cells and BCR-ABL-induced chronic myeloid leukemia and acute lymphoblastic leukemia in mice. *Leukemia*. 2009;23(8):1446-1454.

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Section 12.1 of the package insert submitted in the NDA states that c-Myc and Cyclin D1 levels are decreased following omacetaxine treatment, but data to support this claim was not provided in the NDA nor is there mention of omacetaxine action on c-Myc or Cyclin D1 levels in the Pharmacology Written Review.

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/s/

M S RICCI

09/05/2012

This review is an Addendum to the Pharmacology and Toxicology Review for NDA 22374 by Dr. Timothy Kropp.

HALEH SABER

09/05/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 203585

Applicant: Cephalon, Inc. (wholly owned subsidiary of Teva Pharmaceuticals) **Stamp Date:** Mar. 30, 2012

Drug Name: Omacetaxine mepesuccinate

NDA/BLA Type: 505(b)(1) NDA;
Previously submitted as NDA 22374, which was not approved

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		6 month tox studies used DP lot #05D08; DS lot #07758 was used to make this DP
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		

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	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	This will determined during the review cycle. No impurity issues were identified during NDA 22374 review that needed toxicology safety evaluation. Since the formulation has changed, the impurity profile may be different.
11	Has the applicant addressed any abuse potential issues in the submission?		X	Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

M. Stacey Ricci, M.Eng., Sc.D.
Reviewing Pharmacologist

May 11, 2012
Date

Haleh Saber, Ph.D.
Team Leader/Supervisor

May 11, 2012
Date

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

/s/

M S RICCI
05/11/2012

HALEH SABER
05/11/2012