Clinical Study Protocol with Amendment 01

An Open-Label, Single-Group Clinical Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Omacetaxine Mepesuccinate Given Subcutaneously as a Fixed Dose in Patients with Chronic Phase or Accelerated Phase Chronic Myeloid Leukemia who have Failed 2 or More Tyrosine Kinase Inhibitor Therapies

Study C41443/2057

NCT02078960

Protocol Amendment 01 Approval Date: 22 April 2015

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Phase 1/Phase 2

Study C41443/2057

IND: 62,384

EudraCT number: 2013-005320-42

Protocol Amendment 01 Approval Date: 22 April 2015

Sponsor
Teva Branded Pharmaceutical Products R&D, Inc.
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Confidentiality Statement

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Conference on Harmonization (ICH); United States (US) Code of Federal Regulations (CFR) and European Union (EU) Directives (as applicable in the region of the study); local country regulations; and the sponsor's Standard Operating Procedures (SOPs).

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AMENDMENT HISTORY

The protocol for study C41443/2057 (original protocol dated 4 December 2013) has been amended and reissued as follows:

Administrative Letter	10 June 2014 No patients enrolled at time of administrative letter.
Amendment 01	22 April 2015 5 patients enrolled to date.

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 01
Original protocol dated 4 December 2013
IND 62,384; EudraCT number: 2013-005320-42
An Open-Label, Single-Group Clinical Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Omacetaxine Mepesuccinate Given Subcutaneously as a Fixed Dose in Patients with Chronic Phase or Accelerated Phase Chronic Myeloid Leukemia who have Failed 2 or More Tyrosine Kinase Inhibitor Therapies

Principal Investigator: [redacted]
Title: [redacted]
Address of Investigational Center: [redacted]

I have read the protocol with Amendment 01 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience and training to conduct this clinical research study. The signature below constitutes approval of this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the drug that were furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the drug and the conduct of the study. I agree to keep records on all patient information, study drug shipment and return forms, and all other information collected during the study, in accordance with local and national Good Clinical Practice (GCP) regulations.

Principal Investigator	Signature [redacted]	Date 4.22.15

Protocol Approval

Sponsor's Authorized Representative [redacted]	Signature [redacted]	Protocol with Amendment 01 Final Date 4/20/15
Coordinating Investigator*	Signature	Date

* Not Applicable In North America [redacted] 23 Apr 2015

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS

Data Management

Pharmaceutical Product Development, LLC (PPD)
7551 Metro Center Drive
Suite 300
Austin, Texas 78744
USA

Central Laboratory for Pharmacokinetic Collection

Information will be provided in the Project Plan.

Interactive Response Technology System

Information will be provided in the Project Plan.

External Data Monitoring Committee

The Data Monitoring Committee (DMC) charter will be included in the Trial Master File when available.

CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the physician listed below:

[redacted]
PPD
[redacted]

For protocol and clinical questions, contact:

[redacted]
Teva Pharmaceuticals
[redacted]

For study operational issues, contact the operational lead listed below:

[redacted]
Teva Pharmaceuticals
[redacted]

For serious adverse events:

Send by facsimile/email to the sponsor's Local Safety Officer/CRO. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.

CLINICAL STUDY PROTOCOL SYNOPSIS

Title of Study: An Open-Label, Single-Group Clinical Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Omacetaxine Mepesuccinate Given Subcutaneously as a Fixed Dose in Patients with Chronic Phase or Accelerated Phase Chronic Myeloid Leukemia who have Failed 2 or More Tyrosine Kinase Inhibitor Therapies

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

Study Number: C41443/2057

Investigational Product: Omacetaxine mepesuccinate (C41443), SYNRIBO®

Phase of Clinical Development: 1/2

Number of Investigational Centers Planned: approximately 40

Countries Planned: Countries in North America and European Union

Number of Patients Planned: Approximately 21 patients are planned for Phase 1. For Phase 2, approximately 45 patient with chronic phase (CP) chronic myeloid leukemia (CML) and 67 patients with accelerated phase (AP) CML are planned to be enrolled.

Study Population: Patients with CP CML or AP CML who have failed 2 or more tyrosine kinase inhibitor (TKI) therapies.

Planned Study Period: Enrollment will start in second quarter 2014 and is expected to be completed in 2016. Patients may undergo up to 1 year of treatment and an additional year of monitoring for survival.

Primary Objectives: The primary objectives of this study are as follows:

- to evaluate the efficacy of omacetaxine when administered subcutaneously as a fixed dose in patients with CP CML or AP CML
- to evaluate the safety of omacetaxine when administered subcutaneously as a fixed dose in patients with CP CML or AP CML
- to characterize the pharmacokinetic profile of omacetaxine in cycle 1 when administered subcutaneously as a fixed dose

Secondary Objectives: The secondary objectives of the study are as follows:

- to determine the duration of responses
- to determine progression-free and overall survival
- to determine molecular response
- to determine additional pharmacokinetic parameters after cycle 1
- to determine additional parameters, such as BCR-ABL transcript

Criteria for Inclusion: Patients may be included in the study only if they meet all of the following criteria:

a. The patient has a confirmed diagnosis of Philadelphia chromosome (Ph) positive chronic myelogenous leukemia in either CP or AP. Accelerated phase will be defined as disease having 1 of the following: ≥15% to <30% blasts in peripheral blood or bone marrow; ≥30% blasts + promyelocytes in peripheral blood or bone marrow; ≥20% basophils in peripheral blood or bone marrow; platelet count $<100 \times 10^9$/L unrelated to therapy; or clonal evolution.

b. The patient has either failed, demonstrated intolerance, or a combination of prior failure and intolerance, to prior treatments with at least 2 tyrosine kinase inhibitors (TKI's). Failure of TKI treatment may either be primary (never achieved a response) or secondary resistance (loss of response).

- TKI treatment failure will be defined as 1 of the following:

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  - no CHR by 12 weeks (whether lost or never achieved)
  - no partial cytogenetic response by 24 weeks (ie, 1 to 35% Ph-positive) (whether lost or never achieved)
  - no major cytogenetic response by 52 weeks (ie, ≤35% Ph-positive) (whether lost or never achieved)
  - progressive leukocytosis, defined as increasing white blood cell (WBC) count on at least 2 consecutive evaluations, at least 2 weeks apart and doubling from the nadir to ≥20000/µL or absolute increase in WBC by ≥50000/µL above the post-treatment nadir
- Intolerance to TKI therapy will be defined as 1 of the following:
  - grade 3 to 4 nonhematologic toxicity that does not resolve with adequate intervention
  - grade 4 hematologic toxicity lasting more than 7 days, or a documented inability to sustain the TKI therapy because of recurrent grade 3 or 4 hematologic toxicity with re-initiation of the same therapy
  - any grade 2 or greater toxicity that is unacceptable to the patient
- Patients with a known T315I mutation must have been treated and failed ponatinib (prior to the entry into this study; this would not apply in a country where ponatinib has not been approved or where patients otherwise would not have access to this medication) unless medically contraindicated by the treating study doctor

c. Patients must have completed all previous anticancer therapy for at least 2 weeks prior to the first planned dose of omacetaxine, except as noted below, and must have fully recovered from side effects of a previous therapy.

- In patients with rapidly proliferating disease, hydroxyurea may be administered before study entry, if clinically indicated, to control disease. In such cases, CHR must be sustained for at least 4 weeks for accelerated CML, and at least 8 weeks for chronic phase CML, following the discontinuation of hydroxyurea, to be considered as a CHR.
- Patients may receive anagrelide for up to 28 days (in countries where the product is registered). Leukapheresis is allowed up to 24 hours prior to the first treatment cycle with omacetaxine.

d. Patients must have adequate hepatic and renal function as evidenced by bilirubin 2.0 times the upper limit of the normal range (ULN) or lower, alanine aminotransferase (ALT) and asparate aminotransferase (AST) 3 times the ULN or lower, serum creatinine 1.5 times the ULN or lower. Patients with nonclinically significant elevations of bilirubin up to 5.0 g/dL (85500 µmol/L) due to known or suspected Gilbert's disease are eligible; this must be documented on the medical history page of the case report form (CRF).

e. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

f. Patients are men or women at least 18 years of age.

g. Patients must be able and willing to provide written informed consent prior to any study related procedure. (In the event that the patient is re-screened for study participation or if a protocol amendment alters the care of an ongoing patient, a new informed consent form must be signed.)

h. Patients must be able to comply with the requirements of the entire study.

i. The patient must take precautions to not become pregnant or produce offspring. Women must be of non-childbearing potential (surgically sterile or postmenopausal for at least 12 months, confirmed by follicle-stimulating hormone [FSH] >40 IU/L) or agree to use a medically accepted method of contraception for the duration of the study and 90 days after treatment. Men must be surgically sterile

or agree to use a medically accepted method of contraception for the duration of the study and 90 days after treatment. Acceptable methods of contraception include abstinence, barrier method with spermicide (excluding cervical cap and sponge), intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method.

Criteria for Exclusion: Patients will be excluded from participating in this study if they meet any of the following criteria:

a. The patient has 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.

b. The patient has had a myocardial infarction in the previous 12 weeks. (Prior to study entry, any other electrocardiogram [ECG] abnormalities noted at screening other than myocardial infarction within the previous 12 weeks and felt by the investigator not to be medically relevant, must be documented as such.)

c. The patient has received radiotherapy within 30 days prior to the start of study drug, or has not recovered from the acute toxicities associated with prior approved therapies including investigational drugs.

d. The patient has another concurrent illness that would preclude study conduct and assessment, including, but not limited to, another active malignancy (excluding squamous or basal cell skin cancer and in situ cervical cancer), uncontrolled medical conditions, uncontrolled and active infection (considered opportunistic, life threatening, or clinically significant), uncontrolled risk of bleeding, or uncontrolled diabetes mellitus.

e. The patient underwent autologous or allogeneic stem cell transplant within 60 days prior to receiving the first dose of omacetaxine and has any evidence of ongoing graft versus host disease (GVHD), or GVHD requiring immunosuppressive therapy.

f. The patient has a human leukocyte antigen (HLA)-matched donor and is eligible for allogeneic transplantation for CML treatment.

g. The patient has known positive human immunodeficiency virus (HIV) or known active human t-cell lymphotropic virus (HTLV) I/II disease, whether on treatment or not.

h. The patient has known active hepatitis B or C. The determination of active hepatitis B or C is left to the investigator.

i. The patient is pregnant or lactating (any women becoming pregnant during the study will be withdrawn from the study).

j. The patient has any medical or psychiatric condition, which may compromise the ability to give written informed consent or to comply with the study protocol.

k. The patient has lymphoid Ph+ blast crisis or blast phase CML.

l. The patient participated in another clinical investigation within 30 days of enrollment or is receiving another investigational agent.

m. The patient received omacetaxine or has a history of hypersensitivity.

n. The patient has a known hypersensitivity to mannitol.

o. The patient has a hemoglobin value, which, in the opinion of the investigator, is not adequate given the pharmacokinetic blood draw requirements of the Phase 1 portion of the study.

p. The patient has undergone major surgery within 14 days prior to starting omacetaxine, or has not recovered from side effects of such procedure.

Study Drug Dose, Mode of Administration, and Administration Rate:

The investigational drug for this study is omacetaxine mepesuccinate. Omacetaxine drug product is a lyophilized vial containing 3.5 mg omacetaxine and 10 mg mannitol in a 10-mL clear glass vial, sealed with rubber stopper and aluminum flip-off seal. Investigational centers will be given vials of 3.5 mg omacetaxine. Omacetaxine will be reconstituted by a healthcare professional. Omacetaxine will be administered by subcutaneous injection at a fixed dose of 2.5 mg twice daily for 7 or 14 consecutive days every 28 days, over a 28-day cycle. The first dose of the day for cycle 1 will be administered at the investigational center. Subsequent doses (in prefilled syringes) may be administered on an outpatient basis after training takes place, unless the patient must come back to obtain more drug or perform test procedures, including pharmacokinetics.

Method of Blinding: This is an open-label study with no blinding.

Duration of Patient Participation: The study will consist of up to a 7-day screening period, and treatment for up to 12 months depending on response and tolerability. Patients will also have an end-of-treatment follow-up visit approximately 28 days (+2 days) after the last dose of omacetaxine. Patients will be monitored for progression and survival for at least 1 year after the last dose of omacetaxine, death, or lost to follow-up, whichever comes first, regardless of patients receiving other anticancer treatment.

General Design and Methodology: This is a Phase 1/Phase 2, open-label, multicenter, single-group clinical study in patients with CP or AP CML who have failed 2 or more TKI therapies to investigate the pharmacokinetic, safety, and efficacy of omacetaxine given subcutaneously as a fixed dose twice daily.

In the Phase 1 portion, there will be 3 cohorts of approximately 7 patients each; patients may have either CP or AP CML. All patients will be given a fixed dose of 2.5 mg omacetaxine subcutaneous injection twice daily. Every effort will be made to include an equal number of patients in each body surface area (BSA) cohort. Cohort 1 will include patients whose BSA is less than 1.7 m^2. Cohort 2 will include patients with a BSA between 1.7 m^2 to 2.0 m^2 inclusive. Cohort 3 will include patients with BSA greater than 2.0 m^2. Based on data from previous clinical research studies, the range of BSA for patients enrolled in those studies was 1.39 to 2.46 m^2 for CP patients, and 1.34 to 2.31 m^2 for AP patients. Because it is known that women usually have a smaller BSA than men, all efforts must be made to include at least 2 men in cohort 1 to reduce possible gender bias. After cycle 1, patients will continue to receive omacetaxine for 12 months until intolerance or disease progression while safety and efficacy parameters are followed.

In the Phase 2 portion, following the analysis of pharmacokinetic and preliminary safety and efficacy data from the patients in Phase 1, a decision whether or not to continue to Phase 2 will be made. If the Phase 1 data indicate that a fixed-dose regimen is not appropriate for subcutaneously administered omacetaxine, enrollment into the Phase 2 portion will be stopped and the study will be terminated. It is anticipated that the analysis of pharmacokinetic and preliminary safety and efficacy data from the patients in Phase 1 will take approximately 2 months. Assuming a fixed-dose regimen is considered appropriate on the basis of the Phase 1 data, a total of up to 45 patients with CP CML and a total of up to 67 patients with AP CML will be enrolled in Phase 2.

In both phases, omacetaxine will be administered by subcutaneous injection twice daily. For cycle 1, the first dose will be administered at the investigational center. Subsequent doses (in prefilled syringes) may be administered on an outpatient basis after training takes place. Patients will be evaluated every 7 days with complete blood and platelet counts up to and including cycle 5 and every 2 weeks (±2 days) after cycle 5; the number of consecutive

doses of omacetaxine or intervals between subsequent cycles may be adjusted, as clinically indicated. Every 3 months (ie, every 3 cycles), bone marrow aspiration and cytogenetics, BCR-ABL transcript measurements, quantitative BCR-ABL kinase domain analysis of peripheral blood, and ECGs will be performed. Note: After a patient achieves a confirmed complete cytogenetic response, RT-PCR BCR-ABL testing should be performed every 6 months unless clinically indicated to do it more often. Patients not demonstrating evidence of clinical response after 6 cycles will be considered for removal from the study; however, with permission of the sponsor's medical monitor, treatment may continue, if clinically indicated, provided there is no evidence of toxicity grade 3 or above. In patients achieving a CHR or major cytogenetic response (MCyR) (either complete cytogenic response [CCyR] or partial cytogenetic response [PCyR]), the response will be confirmed by a repeat complete blood count (CBC), bone marrow aspiration (for patients with a hematologic response), cytogenetics of the bone marrow aspirate (for patients with a cytogenetic response), and BCR-ABL transcript levels by quantitative reverse transcription-polymerase chain reaction (RT-PCR) of peripheral blood. Confirmations are to be performed at least 8 weeks after the initial documentation of response for patients with CP CML and at least 4 weeks after the initial documentation of response for patients with AP CML. If the CBC, bone marrow aspiration, and/or cytogenetic results do not confirm the clinical response and the patient is already on maintenance treatment cycles, the patient may continue on maintenance therapy or may revert back to induction cycles (ie, 14 days of omacetaxine treatment) or the highest number of days tolerated previously, if clinically indicated. Patients who demonstrate CHR, hematologic improvement (HI), or any cytogenetic response, may convert from induction to maintenance therapy.

Primary Efficacy Variables and Endpoints: The primary efficacy variable for patients with CP CML is the proportion of patients who achieve a MCyR (CCyR with no Ph+ metaphases and PCyR with 1 to 35% Ph+ metaphases). The primary efficacy variable for patients with AP CML is the proportion of patients who achieve a major hematologic response (MaHR: complete hematologic response or no evidence of leukemia) and/or MCyR.

Secondary Efficacy Variables and Endpoints:

The secondary efficacy variables and endpoints for this study are as follows:

- duration of response, defined for responders as the time interval from the first reported date of MCyR or MaHR, as defined above, to the earliest date of objective evidence of disease progression (ie, development of accelerated-phase CML), relapse (ie, loss of complete hematologic or major cytogenetic response), or death
- molecular response by site (peripheral transcript of BCR-ABL)
- progression-free survival, defined as the time interval from date of first dose to earliest date of objective evidence of disease progression (ie, development of AP CML), relapse (ie, loss of complete hematologic or major cytogenetic response), or death
- overall survival, defined as the time interval from date of first dose to date of death from any cause

Safety Variables and Endpoints: The safety and tolerability of omacetaxine treatment will be assessed throughout the study by evaluating the following safety variables:

- adverse events (type, frequency, severity, and causality)
- clinical laboratory test results (serum chemistry and hematology) at various points in the study
- exploratory predictors of toxicity such as myelosuppression to assist with safety signals
- vital signs measurements (blood pressure, heart rate, respiratory rate, body temperature)
- physical examination (including weight)
- 12-lead ECG
- concomitant medication usage

Pharmacokinetics: The following pharmacokinetic parameters for omacetaxine and its metabolites will be calculated for each patient, when possible, from plasma concentrations obtained following the first dose of omacetaxine in Phase 1:

- maximum observed plasma drug concentration (C_{max}) by inspection (without interpolation)
- time to C_{max}, by inspection (t_{max})
- area under the drug concentration by time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$)
- AUC from time 0 to the time of the last measurable drug concentration (AUC_{0-t})
- AUC from time 0 to 12 hours (AUC_{0-12})

- apparent plasma terminal elimination rate constant (λ_z) and associated terminal elimination half-life ($t_{½}$)
- percentage extrapolation calculated as $(AUC_{0-\infty}-AUC_{0-t})/(AUC_{0-\infty})x100$
- apparent plasma clearance (CL/F)
- apparent volume of distribution (V_z/F)
- predicted accumulation ratio (R_{pred}) calculated as $AUC_{0–\infty}/AUC_{0–12}$

In Phase 1, to accommodate the pharmacokinetic objective of the study, during cycle 1, omacetaxine will be administered by subcutaneous injection as follows: 1 dose will be administered in the morning of day 1, no doses will be administered on days 2 or 3, 2 doses will be administered on days 4 through 17. Blood samples (2.5 mL) will be obtained during Phase 1 as follows:

- 20 minutes prior to and 15 (±5 min), 30 (±5 min), and 45 (±5 min) minutes and 1 (±5 min), 2 (±10 min), 4 (±10 min), 8 to 12 (±15 min), 24 (±1 hr), 48 (±1 hr), and 72 (±1 hr) hours (predose 1 on day 4) after administration of the first dose of omacetaxine
- on day 10 or 11 or 12, predose within (<) 1 hour after dose 1, and 1 to 12 hours after dose 1
- 1 sample on day 13, 14, 15, 16, or 17 either predose 1 or predose 2

In addition, blood samples (2.5 mL) will be obtained in Phase 1 on day 1 of cycles 2 and 3 and in Phase 2 on day 1 of cycles 1, 2, and 3 as follows:

- within (<) 1 hour after dose 1
- 1 to 12 hours after dose 1
- 1 sample either predose 1 or predose 2 on any day after day 1 during week 1
- 1 sample either predose 1 or predose 2 on any day during week 2

Statistical Considerations: The sample size for Phase 1 is approximately 21 patients in order to meet the pharmacokinetic objectives of the study. These 21 patients will also be counted in the sample size for Phase 2 and be part of any Phase 2 analyses. Phase 2 sample sizes are based on Simon's 2-stage optimum design. To reject the null hypothesis of MCyR rate 2.5% or lower in patients with CP CML at a target 1-sided alpha of 0.025 and beta of 0.10 (power of 90%) and assuming that the MCyR rate in the current study will be at least 16%, in the first stage 16 patients with CP CML will be treated. If 1 or more patients respond, then the study will enroll another 29 patients with CP CML for a total of 45 patients. If 4 or more of the 45 patients achieve a MCyR, the fixed-dose regimen will be deemed effective in patients with CP CML. If the true rate is less than or equal to 2.5%, the probability of stopping after stage 1 is 0.667. The alternative hypothesis rate is set at 16% because an 18.4% response rate was observed in the registration studies (Studies CGX-635-CML-202 and CGX-635-CML-203) in which patients received older generations of TKI drugs, and in the current study patients will be more likely to have received a newer generation of TKI drugs and more lines of therapy and may be less likely to respond to omacetaxine. To reject the null hypothesis of MCyR rate 2.5% or lower in patients with AP CML at a target 1-sided alpha of 0.025 and beta of 0.10 (power of 90%), and assuming that the MaHR rate in the current study will be at least 12%, in the first stage 40 patients with AP CML will be treated. If 2 or more patients achieve a MaHR, then the study will enroll another 27 patients with AP CML for a total of 67 patients. If 5 or more of the 67 patients respond, then the drug will be deemed to be effective in patients with AP CML. If the true rate is 2.5% or lower, the probability of stopping after stage 1 is 0.736. The alternative hypothesis rate is set at 12%, lower than the observed rate of 14.3 in the above mentioned registration studies for the same reason. Response rates by disease phase (CP CML and AP CML) and their 2-sided exact 95% confidence intervals (CIs) will be calculated. The lower limit of the CI will be compared with a prior value of 2.5%. If the lower limit exceeds 2.5%, the observed response rate will have exceeded the minimum threshold required to demonstrate efficacy. When sample size permits, these variables will also be compared within a disease phase by age, sex, disease history, and treatment history using a logistic regression model.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
βHCG	beta human chorionic gonadotropin
λz	terminal elimination rate constant
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
AP	accelerated phase
APL	acute promyelocytic leukemia
AST	aspartate aminotransferase
AUC	area under the drug concentration by time curve
AUC_{0-t}	area under the drug concentration by time curve from time 0 to the time of the last measurable drug concentration
AUC_{0-12}	area under the drug concentration by time curve from time 0 to 12 hours
$AUC_{0-\infty}$	area under the drug concentration by time curve from time 0 to infinity
bid	twice daily
BP	blood pressure/blast phase
BSA	body-surface area
BUN	blood urea nitrogen
CBC	complete blood count
CDMS	clinical data management system
CEC	Central Ethics Committee
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CHR	complete hematologic response
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	clinical leader
CL/F	total oral clearance
C_{max}	maximum observed plasma drug concentration
CML	chronic myeloid leukemia
CO_2	carbon dioxide

Abbreviation	Term
CP	chronic phase
CPP	clinical project physician
CR	complete response
CRF	case report form
CRO	contract research organization
CYP450	cytochrome P450
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FDA	US Food and Drug Administration
FISH	florescence in situ hybridization
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HCG	human chorionic gonadotropin
HI	hematologic improvement
HIV	human immunodeficiency virus
HR	heart rate
hr	hour
HTLV	human t-cell lymphotropic virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
LSO	local safety officer
MaHR	major hematologic response
MCyR	major cytogenic response
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
min	minute
ms	milliseconds
NA	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEL	no evidence of leukemia
NYHA	New York Heart Association
NSAIDS	non-steroidal anti-inflammatory drugs
PCR	polymerase chain reaction
PCyR	partial cytogenic response
P-gp	P-glycoprotein
Ph	Philadelphia
Ph+	Philadelphia chromosome-positive
PMR	postmarketing requirement
PPD	Pharmaceutical Product Development, LLC
RBC	red blood cell
R_{pred}	predicted accumulation ratio
RR	respiratory rate
RT-PCR	reverse transcription-polymerase chain reaction
SD	standard deviation
SDV	source data verification
SOPs	standard operating procedures
T	temperature
TKI	tyrosine kinase inhibitor
$t_{½}$	terminal elimination half-life
t_{max}	time to maximum observed plasma drug concentration
ULN	upper limit of the normal range
US(A)	United States (of America)
V_z/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WHO Drug	World Health Organization (WHO) drug dictionary
XML	extensible markup language

1. BACKGROUND INFORMATION

1.1. Introduction

1.1.1. Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a myeloproliferative disorder that can occur with a bi- or tri-phasic course. CML occurs with an incidence of about 1 to 1.5 cases per 100000 population and accounts for about 7% to 15% of newly diagnosed cases of leukemia in adults. Major geographic or ethnic differences are insignificant. The median age at diagnosis is 64 years in the United States of America (USA). The median age at diagnosis ranges between 60 and 65 years in Europe. It is lower in countries where the population is younger (Baccarani et al 2012). The median survival is 4 to 6 years, with a range of less than 1 year to more than 10 years. The overall 5-year relative survival for 2003 to 2009 was 59% (http://seer.cancer.gov/csr/1975_2010/). Survival after development of an accelerated phase is usually less than 1 year and after blastic transformation is only a few months.

The typical tri-phasic course of disease is characterized by an initial chronic phase (CP) lasting 3 to 6 years, followed by an accelerated phase (AP), then blast phase (BP) usually of short duration. Seventy-five percent to 80% of patients go through an accelerated phase before the blastic phase. The definition for accelerated phase is not uniform. Specific criteria associated with a survival less than 18 months by multivariate analysis have been proposed, including the presence of 15% or more blasts, or 30% or more blasts and promyelocytes, or 20% or more basophils in the blood, or platelet count less than $100x10^9$/L. A cytogenetic clonal evolution is also considered a criterion for acceleration. Recent analysis suggests its prognostic effect depends on the specific abnormality, its predominance in marrow metaphases, and the time of appearance. Secondly, major studies use the definition for AP CML as in the inclusion criteria of this protocol (blasts in blood or bone marrow ≥15%) rather than 20% or more blasts. The reason is due to the lack of data for the definition of when AP CML is categorized differently. Data showed that patients with 20% to 29% blasts have an outcome similar to patients with AP criteria, as defined above, having a median survival approximately 12 months longer than those with blasts more than or equal to 30% (Cortes and Kantarjian 2012).

The cytogenetic hallmark of CML is a reciprocal t(9;22)(q34;q11) chromosomal translocation that creates a derivative 9q+ and a small 22q–, known as the Philadelphia (Ph) chromosome. The latter harbors the BCR-ABL fusion gene encoding a chimeric BCR-ABL protein with a deregulated tyrosine kinase activity, the expression of which has been shown to be necessary and sufficient for the transformed phenotype of CML cells. The activation of multiple signal transduction pathways in BCR-ABL–transformed cells leads to increased proliferation, reduced growth-factor dependence and apoptosis, and perturbed interaction with extracellular matrix and stroma. It is thought that the expression of BCR-ABL endows a pluripotent hematopoietic progenitor cell and/or its progeny with a growth and survival advantage over normal cells, which in time leads to clinical manifestation of CML. CML is unusual among malignancies in humans in that a single oncogene product has been identified as playing a central role in its pathology.

As BCR-ABL kinase, the product of the Philadelphia chromosome, plays an obligatory role in the pathogenesis of CML, there was a strong theoretical rational for targeting this function therapeutically. This ultimately led to the development and approval of imatinib mesylate (STI-571, GLEEVEC™, GLIVEC®, Novartis Pharmaceuticals Corporation), an inhibitor of BCR-ABL kinase activity. The clinical success of imatinib mesylate in treatment of CML, especially the high durable response rates in patients with CP CML, has validated the therapeutic strategy of rationally targeting the causative molecular abnormality of CML, and changed the management of the disease.

1.1.2. Resistance to Tyrosine Kinase Inhibitors

Resistance to imatinib is now well documented. The most common mechanism of acquired imatinib resistance is the reactivation of BCR-ABL kinase activity within the leukemic cell, despite the presence of imatinib. Two underlying mechanisms account for this, either gene amplification or point mutation in the BCR-ABL kinase domain.

Although many point mutations in the BCR-ABL kinase domain have now been described, amino acids 315 and 253 have been found to be critical for efficient imatinib binding. Mutations of these 2 amino acids, along with amino acids 255 and 351, were subsequently identified in 60% of patients with kinase domain mutations at the time of disease relapse, with an overall mutation frequency between 30% and 90%. The marked decrease in sensitivity of these mutants to imatinib implicates them as the likely cause of resistance.

New tyrosine kinase inhibitors have been developed to overcome resistance to imatinib, including dasatinib (SPRYCEL®, Bristol-Myers Squibb), nilotinib (TASIGNA®, Novartis Pharmaceuticals Corporation), bosutinib (BOSULIF®, Pfizer Laboratories), and ponatinib (ICLUSIG®, Ariad Pharmaceuticals, Inc.). Dasatinib and nilotinib are both approved for use in patients with newly diagnosed CP CML, while bosutinib and ponatinib have been approved for patients with CML in all 3 phases with resistance or intolerance to prior therapy. Through their sequential use, these kinase inhibitors have extended the overall survival of patients with CML. However, eventually patients will relapse and new treatments are continually being sought.

Omacetaxine mepesuccinate (omacetaxine) has demonstrated activity in both early and late CP CML, as well as other hematologic malignancies, including acute promyelocytic leukemia (APL), acute myelogenous leukemia (AML), and myelodysplastic syndrome (MDS).

Omacetaxine works via a different mechanism than the kinase inhibitors. Omacetaxine inhibits protein synthesis and binds to the A-site cleft in the peptidyl-transferase center of the large ribosomal subunit. In vitro, omacetaxine reduced protein levels of the BCR-ABL oncoprotein and Mcl-1, an anti-apoptotic Bcl-2 family member. Omacetaxine has also shown activity in mouse models of wild-type and T315I mutated BCR-ABL CML. In patients with CP CML having the T315I mutation, and after failing treatment with tyrosine kinase inhibitors (TKIs), omacetaxine showed clinical activity (Cortes et al 2012).

Therefore, patients with CML who have failed or are intolerant to prior treatment with TKIs may still respond to treatment with omacetaxine. Based on the study results for patients with CP and AP CML who failed TKIs, the US Food and Drug Administration (FDA) approved omacetaxine

for the patients in these 2 phases of CML. SYNRIBO® (omacetaxine mepesuccinate) for injection for subcutaneous use is indicated for the treatment of adult patients with CP or AP CML with resistance and/or intolerance to 2 or more TKIs. This indication is based upon response rate. There are no studies verifying an improvement in disease-related symptoms or increased survival with SYNRIBO (Package insert Oct 2012 version www.fda.gov).

1.1.3. Rationale for the Study

In oncology, the dosage of nearly all cytotoxic drugs is based on body-surface area (BSA) of the patient (Field et al 2008, Mathijssen et al 2007). However, fixed or "flat dosing", using a single dose for all patients regardless of BSA or weight may offer advantages with regard to administration dose errors and patient safety for a drug given subcutaneously. To satisfy a postmarketing requirement (PMR), the sponsor has been requested by FDA to conduct a Phase 1/Phase 2 open label clinical study to investigate the pharmacokinetics and preliminary safety and efficacy of omacetaxine following a fixed-dose administration to patients with CP or AP CML who have failed 2 or more TKI therapies. Therefore, this study was designed for the same patient population for which omacetaxine was approved but with a "fixed or flat" dosing approach. If this approach proves safe and efficacious as in the registration trials, this would prove to be a benefit to patients and healthcare providers to ensure or avoid less dosing errors when given subcutaneously and improve patient compliance due to improved ease of administration.

Additionally, this study was requested since the pharmacokinetics of omacetaxine may or may not be related to BSA. A BSA-based dose could result in lower drug concentrations and potentially reduced efficacy in patients with traditionally lower BSAs, such as women, as women have lower body surface areas. Lower exposures may contribute to reported observations of a lower response rate in women. Therefore, a fixed dose may increase exposure in any patients with low BSA and potentially optimize their probability of response. This PMR study may assist to optimize the dosing regimen in future trials.

A population pharmacokinetic model was developed for omacetaxine using the pharmacokinetic data collected in Study CGX-635-205 and it was used to predict individual measures of omacetaxine exposure in patients enrolled in Studies CGX-635-202 and CGX-635-203, respectively. Study CGX-635-205 assessed pharmacokinetics and safety of subcutaneous omacetaxine in patients with advanced cancers, and had results recently published (Nemunaitis et al 2013). The relationships between these individual exposure estimates and efficacy and selected safety endpoints were investigated. These exposure-response relationships were used to simulate anticipated outcomes, with data from the CML registration Studies CGX-635-202 and CGX-635-203, respectively, with various fixed treatment regimens. The registration studies did not have pharmacokinetics in their study design.

A comparison of fixed-doses between 2 and 3.5 mg, without regard to BSA, illustrates that there is potential benefit in terms of an increased predicted probability of efficacy with a dose of

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2.5 mg over a 2 mg dose (almost 3-fold increase in the predicted probability of major hematologic response [MaHR] and almost 2-fold increase in the predicted probability of major cytogenic response [MCyR]) (data on file). The 3 mg dose is associated with an even greater predicted probability of efficacy in both the AP and CP populations. The increased risk associated with these doses, in terms of the predicted probability of experiencing grade 3 or grade 4 thrombocytopenia, over the 2 mg dose, is small on the basis of the simulation data, but not fully understood due to the limited size of the CGX-635-205 dataset.

The 3.5 mg dose, which represents a higher dose than any administered in Studies CGX-635-205, CGX-635-CML-202, or CGX-635-CML-203, is predicted to provide only a small additional improvement in the probability of efficacy and in the risk of neutropenia over the 3 mg alternative, and also a slightly increased risk of thrombocytopenia over the 3 mg alternative; and it comes with the added uncertainty of being outside the range of previously tested doses. Therefore, administration of this dose is not recommended.

Because the number of patients in Study CGX-635-205 was small, the predictions from this population pharmacokinetic modeling must be used with caution. On the basis of the data currently available, the impact of fixed dose on the benefit-risk profile in patients with CML who have failed TKI therapy remains unknown. For this reason, a fixed dose of 2.5 mg twice daily was selected because it approximates to the dose that would have been given to a patient of median BSA under the current 1.25 mg/m^2 twice daily regimen. In the phase 1 portion of the study, a sample size of approximately 21 patients enrolled in cohorts of small, medium, and large BSA is considered sufficient to properly characterize the pharmacokinetics of the 2.5 mg twice daily fixed dose.

1.2. Name and Description of Investigational Product

SYNRIBO (omacetaxine mepesuccinate) for injection, for subcutaneous use, was approved by the US FDA on 26 October 2012. It is a semi-synthetic version of a plant alkaloid extracted from *Cephalotaxus fortunei*, a species of evergreen tree that is indigenous to China. The chemical name for omacetaxine mepesuccinate is cephalotaxine, 4-methyl-2-hydroxy-2-(4-hydroxy-4-methylpentyl) butanedioate ester. It has a chemical formula of $C_{29}H_{39}NO_9$ and a molecular weight of 545.6 g/mol. The mechanism of action of omacetaxine mepesuccinate has not been fully elucidated but includes inhibition of protein synthesis and is independent of direct BCR-ABL binding.

The investigational product in this study is referred to in this document as either omacetaxine or omacetaxine mepesuccinate. A more detailed description of the product is given in Section 3.4 and in the current Investigator's Brochure.

1.3. Findings from Nonclinical and Clinical Studies

1.3.1. Nonclinical Studies: Carcinogenesis and Genotoxicity

No carcinogenicity studies have been conducted with omacetaxine mepesuccinate. Omacetaxine mepesuccinate was genotoxic in an in vitro chromosomal aberration test system in Chinese

hamster ovary (CHO) cells, but was not mutagenic when tested in an in vitro bacterial cell assay (Ames test), and it did not induce genetic damage using an in vivo mouse micronucleus assay.

For information on other nonclinical studies see the Investigator's Brochure.

1.3.2. Clinical Studies of Subcutaneous Omacetaxine in CML

Omacetaxine is a semi-synthetic plant alkaloid initially tested in China. Omacetaxine has shown activity in CML and other hematologic cancers, including APL, AML, and MDS.

Several studies have been conducted of subcutaneous administration of omacetaxine in CML. These are summarized in the following sections.

1.3.2.1. Phase 1/Phase 2 Dose Response Study of Subcutaneous Omacetaxine (Study T99-0044)

A Phase 1 study of subcutaneous omacetaxine was conducted under Investigational New Drug (IND) 19,125 in patients with CML at the MD Anderson Hospital. Sixteen patients in accelerated (AP; n=2), blast (BP; n=8), or late chronic (CP, n=6) phase CML were treated. All patients received an initial intravenous loading dose of omacetaxine over 24 hours, followed by twice daily subcutaneous administration at 1of the following dose levels: 0.5, 1.0, or 1.25 mg/m^2 twice daily (except for the intravenous loading dose that was given as 1 dose over 24 hours, equivalent to 2 subcutaneous doses). The latter dose (1.25 mg/m^2 twice daily) was the same dose of omacetaxine as had been used intravenously in prior CML studies, and thus no further dose escalation was pursued beyond this point.

Three patients were treated at the lowest dose level (1 cycle each), and none experienced any nonhematologic toxicity. Three patients were treated at 1.0 mg/m^2 (1 cycle each); only grade 1 toxicity (1 each: nausea, diarrhea, headache) was observed. Four patients received 1.25 mg/m^2 (1 cycle in 2 patients, 2 cycles in 1 patient, and 3 cycles in 1 patient); toxicity included grade 1 diarrhea (n=3), grade 1 abdominal pain (n=1), grade 2 nausea (n=2), and grade 2 anorexia, mucositis, allergic reaction, fatigue, and vomiting (n=1 each).

One complete response (CR) and 1 stable disease have been observed. Three patients had a 1-log reduction in peripheral blood basophils (n=2; 2.37 to 0.25x10^9/L and 8.2 to 0.13x10^9/L) or blasts (n=1; 6.7 to 0.5x10^9/L), and 2 others had a more than 50% reduction in peripheral blood basophils (5.6 to 3.2x10^9/L) or blasts (91.5 to 44.5x10^9/L). Three of these responses occurred among the 4 patients treated at the highest omacetaxine dose level, 1.25 mg/m^2 subcutaneous twice daily. Based on the observations from the initial 10 patients in this study, it was concluded that omacetaxine administered by the subcutaneous route was safe and had clinical activity in patients with CML.

Additionally, 6 patients who had been previously treated with imatinib mesylate were treated with omacetaxine at 1.25 mg/m^2 subcutaneous twice daily for 7 days every month. All of the 5 evaluable patients in this phase achieved a complete hematologic response (CHR); the longest duration of observed response was 8 months. Two (40%) patients achieved a complete and minor cytogenetic response, respectively. One patient had both G250E and Y253H mutations present,

and the other had a single D276G mutation. Subsequent to omacetaxine therapy, these BCR-ABL point mutations were not observed in either patient. These results provide encouraging evidence that omacetaxine may exhibit particular efficacy in this group of patients.

1.3.2.2. Phase 2 Studies of Omacetaxine in Patients with CP CML and AP CML Following Failure of Tyrosine Kinase Inhibitor (TKI) Therapy

The efficacy of subcutaneously administered omacetaxine was evaluated using a combined cohort of adult patients with CML from 2 studies (CGX-635-CML-202 and CGX-635-CML-203). The combined cohort consisted of patients who had received 2 or more approved TKIs and had, at a minimum, documented evidence of resistance or intolerance to dasatinib and/or nilotinib. Resistance was defined as 1 of the following: no CHR by 12 weeks (whether lost or never achieved); or no cytogenetic response by 24 weeks (ie, 100% Ph positive [Ph+]) (whether lost or never achieved); or no MCyR by 52 weeks (ie, ≥35% Ph+) (whether lost or never achieved); or progressive leukocytosis. Intolerance was defined as 1 of the following: 1) grade 3 or 4 nonhematologic toxicity that did not resolve with adequate intervention; 2) grade 4 hematologic toxicity lasting more than 7 days; or 3) any grade 2 or greater toxicity that was unacceptable to the patient. Patients with New York Heart Association [NYHA] class III or IV heart disease, active ischemia, or other uncontrolled cardiac conditions were excluded.

Patients were treated with omacetaxine mepesuccinate at a dose of 1.25 mg/m^2 administered subcutaneously twice daily for 14 consecutive days every 28 days (induction cycle). Responding patients were then treated with the same dose and twice daily schedule for 7 consecutive days every 28 days (maintenance cycle). Patients were allowed to continue to receive maintenance treatment for up to 24 months. Responses were adjudicated by an independent Data Monitoring Committee (DMC).

A total of 76 patients with CP CML were included in the efficacy analysis. The demographics were: median age 59 years; 62% were male; 30% were 65 years of age or older; 80% were Caucasian, 5% were African-American, 4% were Asian, and 4% were Hispanic. Thirty-six (47%) patients had failed treatment with imatinib, dasatinib, and nilotinib. Most patients had also received prior non-TKI treatments, most commonly hydroxyurea (54%), interferon (30%), and/or cytarabine (29%).

A total of 14 (18.4%) patients achieved a MCyR, including 6 patients with a confirmed complete cytogenic response (CCyR) and 3 patients with a confirmed partial cytogenic response (PCyR). 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).

A total of 35 patients with AP CML were included in the efficacy analysis. The demographics were: median age was 63 years; 57% were male; 46% were 65 years of age or older; 68% were Caucasian, 23% were African-American, 3% were Asian, and 3% were Hispanic. Twenty-two (63%) of 35 patients with AP CML had failed treatment with imatinib, dasatinib, and nilotinib. Most patients had also received prior non-TKI treatments, most commonly hydroxyurea (43%), interferon (31%), and/or cytarabine (29%). The efficacy endpoint was assessed based on MCyR and MaHR (CHR or no evidence of leukemia [NEL]).

A total of 5 (14.3%) patients achieved a MaHR, including 4 patients with a CHR and 1 patient with NEL. 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).

1.3.3. Clinical Safety and Tolerability

The following safety and tolerability data are summarized from the studies of subcutaneously administered omacetaxine in adult patients with CML who had received 2 or more approved TKIs (studies CGX-635-CML-202 and CGX-635-CML-203), which are the studies on which the approval of SYNRIBO was based.

1.3.3.1. Chronic Phase CML

Adverse events were reported for 99% of the patients with CP CML. A total of 18% of patients had adverse events leading to withdrawal. The most frequently occurring adverse events leading to withdrawal were pancytopenia, thrombocytopenia, and increased alanine aminotransferase (ALT) (each 2%). A total of 87% of patients reported at least 1 grade 3 or grade 4 treatment emergent adverse event. Serious adverse events were reported for 51% of patients. Serious adverse events reported for at least 5% of patients were bone marrow failure and thrombocytopenia (each 10%), and febrile neutropenia (6%). Serious adverse events of infections were reported for 8% of patients. Deaths occurred while on study in 5e (5%) patients with CP CML. Two patients died due to cerebral hemorrhage, 1 due to multi-organ failure, 1 due to progression of disease, and 1 from unknown causes.

The most commonly reported nonhematologic adverse events (≥20%) were infections (46%), diarrhea (42%), infusion and injection site reactions (34%), nausea (32%), fatigue (26%), pyrexia (24%), and asthenia (23%). The most commonly reported grade 3 or 4 nonhematologic adverse events (≥2%) were infections (11%), fatigue (5%), and back pain (2%). The most common (≥10%) grade 3 or 4 laboratory findings were platelets decreased (85%), neutrophils decreased (81%), leucocytes decreased (72%), hemoglobin decreased (62%), uric acid increased (56%), and glucose increased (10%).

1.3.3.2. Accelerated Phase CML

Adverse events regardless of investigator attribution were reported for 100% patients with AP CML. A total of 33% of patients had adverse events leading to withdrawal. The most frequently occurring adverse events leading to withdrawal were leukocytosis (6%), and thrombocytopenia (4%). A total of 84% of patients reported at least 1 grade 3 or grade 4 treatment emergent adverse event. Serious adverse events were reported for 60% of patients. Serious adverse events reported for at least 5% of patients were febrile neutropenia (18%), thrombocytopenia (9%), anemia (7%), and diarrhea and convulsions (6% each). Serious adverse events of infections were reported for 11% of patients. Death occurred while on study in 5 (9%) patients with AP CML. Two patients died due to cerebral hemorrhage and 3 due to progression of disease.

The most commonly reported nonhematologic adverse events (≥20%) were infections (56%), diarrhea (35%), fatigue (31%), pyrexia (29%), nausea (27%), asthenia (24%), and infusion and

injection site events (22%). The most commonly reported nonhematologic grade 3 or 4 adverse events (≥2%) were infections (20%), fatigue (9%), diarrhea (7%), nausea (4%), and vomiting, pyrexia, asthenia, anorexia, pain in extremity, dyspnea, and epistaxis (2% each). The most common (≥10%) grade 3 or 4 laboratory findings were platelets decreased (88%), hemoglobin decreased (80%), neutrophils decreased (71%), leucocytes decreased (61%), uric acid increased (57%), creatinine increased (16%), and glucose increased (10%).

1.3.4. Clinical Pharmacology

The dose proportionality of omacetaxine mepesuccinate is unknown. A 90% increase in systemic exposure to omacetaxine mepesuccinate was observed between the first dose and steady state.

Absorption: The absolute bioavailability of omacetaxine mepesuccinate has not been determined. Omacetaxine mepesuccinate is absorbed following subcutaneous administration, and maximum concentrations are achieved after approximately 30 minutes.

Distribution: The steady-state (mean ±standard deviation [SD]) volume of distribution of omacetaxine mepesuccinate 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 mepesuccinate is less than or equal to 50%.

Metabolism: Omacetaxine mepesuccinate is primarily hydrolyzed to 4′-DMHHT via plasma esterases with little hepatic microsomal oxidative and/or esterase-mediated metabolism in vitro.

Elimination: The major elimination route of omacetaxine mepesuccinate is unknown. The mean percentage of omacetaxine mepesuccinate excreted unchanged in the urine is less than 15%. The mean half-life of omacetaxine mepesuccinate following subcutaneous administration is approximately 6 hours.

Drug Interactions: Omacetaxine mepesuccinate is not a substrate of cytochrome P450 (CYP450) enzymes in vitro. Omacetaxine mepesuccinate and 4′-DMHHT do not inhibit major CYPs in vitro at concentrations that can be expected clinically. The potential for omacetaxine mepesuccinate or 4′-DMHHT to induce CYP450 enzymes has not been determined. Omacetaxine mepesuccinate is a P-glycoprotein (P-gp) substrate in vitro. Omacetaxine mepesuccinate and 4′-DMHHT do not inhibit P-gp mediated efflux of loperamide in vitro at concentrations that can be expected clinically.

Assessment of Risk for QT Prolongation: In an uncontrolled pharmacokinetic study there were no reports of QTcF greater than 480 milliseconds (ms) or change of QTcF greater than 60 ms in 21 patients who received omacetaxine mepesuccinate 1.25 mg/m^2 twice daily (bid) for 14 consecutive days. There was no evidence for concentration-dependent increases in QTc for omacetaxine mepesuccinate or 4'-DMHHT. Although the mean effect on QTc was 4.2 ms (upper 95% confidence interval [CI]: 9.5 ms), QTc effects less than 10 ms cannot be verified due to the absence of a placebo and positive controls.

For more updated information please refer to the current Investigator's Brochure.

1.3.5. Justification for Study Treatment Plan

The purpose of this current study is to evaluate the pharmacokinetics and the preliminary safety and efficacy of a fixed-dose regimen of omacetaxine (2.5 mg BID sc) for the treatment of patients with CP or AP CML following failure of TKI therapy. For this reason, the treatment plan is the same as that used in the Phase 2 registration studies for omacetaxine (Studies CGX-635-CML-202 and CGX-635-CML-203) with a fixed dose being used in place of doses adjusted for BSA and with the precautions to minimize toxicity and improve tolerability as described in Section 1.4 called Known and Potential Risks and Benefits to Human Patients. As an additional precaution for unforeseeable risks, an independent DMC that will evaluate safety, pharmacokinetics, and efficacy, has been implemented from the beginning of the study including the phase 1 portion as defined in its charter.

The study treatment plan includes recommendations for supportive therapies and management of toxicities, including hematologic toxicity, if necessary. Refer please, to Section 3 and Section 5 of the protocol CEP 41443/2057 for full details.

1.4. Known and Potential Risks and Benefits to Human Patients

Subcutaneous administration of omacetaxine resulted in an 18.4% MCyR rate in patients with CP CML, with a median duration of response of 12.5 months. In patients with AP CML a MaHR rate of 14.3% was achieved with a median duration or response of 4.7 months.

Myelosuppression: In uncontrolled studies with omacetaxine, patients with chronic phase and AP CML experienced National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (version 3.0) grade 3 or grade 4 thrombocytopenia (85%, 88%, respectively), neutropenia (81%, 71%, respectively), and anemia (62%, 80%, respectively). Fatalities related to myelosuppression occurred in 3% of patients in the safety population (N=163). Patients with neutropenia are at increased risk for infections, and should be monitored frequently and advised to contact a physician if they have symptoms of infection or fever. In clinical studies, myelosuppression was generally reversible and usually managed by delaying the next cycle and/or reducing days of treatment with omacetaxine.

Bleeding: Omacetaxine causes severe thrombocytopenia which increases the risk of hemorrhage. In clinical studies in patients with CP and AP CML, a high incidence of grade 3 and grade 4 thrombocytopenia (85% and 88%, respectively) was observed. Fatalities from cerebral hemorrhage occurred in 2% of patients treated with omacetaxine in the safety population. Severe, non-fatal, gastrointestinal hemorrhages occurred in 2% of patients in the same population. Most bleeding events were associated with severe thrombocytopenia.

Hyperglycemia: Omacetaxine can induce glucose intolerance. Grade 3 or grade 4 hyperglycemia was reported in 11% of patients in the safety population. Hyperosmolar non-ketotic hyperglycemia occurred in 1 patient treated with omacetaxine in the safety population.

Embryo-Fetal Toxicity: Omacetaxine can cause fetal harm when administered to a pregnant woman. Omacetaxine mepesuccinate caused embryo-fetal death in animals.

Additional information regarding risks and benefits to human patients may be found in the current Investigator's Brochure.

1.5. Selection of Drugs and Dosages

The purpose of this study is to investigate the pharmacokinetic and preliminary safety and efficacy of omacetaxine following fixed-dose administration in patients with CP or AP CML who have failed 2 or more TKI therapies. The ultimate goal is to investigate whether a fixed dose, administered subcutaneously, may be used to treat patients with CP and AP CML effectively, with no worsening of the safety profile and no loss of efficacy.

In order to address variation in BSA, patients will be enrolled in cohorts according to BSA. In Phase 1, there will be 3 cohorts, approximately 7 patients each. All patients will be given a fixed dose of 2.5 mg bid subcutaneous injection. Every effort will be made to include equal numbers of patients across all BSA cohorts. Cohort 1 will include patients whose BSA is less than 1.7 m^2. Cohort 2 will include patients with a BSA between 1.7 m^2 to 2.0 m^2 inclusive. Cohort 3 will include patients with BSA greater than 2.0 m^2. Based on previous data from clinical research studies, the range of BSA for patients enrolled in those studies was 1.39 m^2 to 2.46 m^2 (median 1.94 m^2) for CP patients, and 1.34 m^2 to 2.31 m^2 (median 1.8 m^2) for AP patients (data on file).

Following the analysis of pharmacokinetic and preliminary safety and efficacy data from the patients in Phase 1, after all have been administered 1 cycle of omacetaxine, a decision will be made whether to move forward to the Phase 2 portion. If patients in Phase 1 tolerate treatment and benefit from therapy, treatment will continue.

A more detailed description of study drug administration is presented in Section 5.1.

1.6. Compliance Statement

This study will be conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, European Union [EU] Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the sponsor and other forms as required by national authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the applicable study staff must be familiar with the

background to, and requirements of, the study and with the properties of the study drug(s) as described in the Investigator's Brochure or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the study at that center and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with local authorities.

1.7. Population To Be Studied

Patients in this study will be men or women, 18 years of age or older, with a confirmed diagnosis of Ph+ CML in either CP or AP. Patients will have either failed, demonstrated intolerance, or a combination of prior failure and intolerance, to prior treatments with at least 2 TKIs. Patients will have adequate hepatic and renal function, controlled blood glucose levels especially in patients with diabetes or risk factors for diabetes, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (see Section 4.1).

1.8. Relevant Literature and Data

Relevant literature is cited above. Further literature and data may be found in the current Investigator's Brochure.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

The purpose of this study is to investigate the pharmacokinetic and preliminary safety and efficacy of omacetaxine treatment following a fixed dose administered subcutaneously in patients with CP or AP CML who have failed 2 or more TKI therapies. The ultimate goal is to investigate a fixed dose to treat patients with CP and AP CML effectively, with no worsening of the safety profile and no loss of efficacy.

2.2. Study Objectives

The primary objectives of the study are as follows:

- to evaluate the efficacy of omacetaxine when administered subcutaneously as a fixed dose in patients with CP CML or AP CML
- to evaluate the safety of omacetaxine when administered subcutaneously as a fixed dose in patients with CP CML or AP CML (see Section 3.2.3)
- to characterize the pharmacokinetic profile of omacetaxine in cycle 1 when administered subcutaneously as a fixed dose (see Section 8)

The secondary objectives of the study are as follows:

- to determine the duration of responses
- to determine progression-free and overall survival
- to determine molecular response
- to determine additional pharmacokinetic parameters after cycle 1
- to determine additional parameters, such as the BCR-ABL transcript

3. STUDY DESIGN

3.1. General Design and Study Schema

This is a Phase 1/Phase 2, open-label, multicenter, single-group clinical study in patients with CP or AP CML who have failed 2 or more TKI therapies designed to investigate the pharmacokinetic, safety, and efficacy of omacetaxine given subcutaneously as a fixed dose.

The study will consist of up to a 7-day screening period, and treatment for up to 12 months, in Phase 1 and Phase 2 portions, depending on response and tolerability. Patients will also have an end-of-treatment follow-up visit approximately 28 days (+2 days) after the last dose of omacetaxine. Each patient will be monitored for progression and survival for at least 1 year after their last dose of omacetaxine, death, or lost to follow-up, whichever comes first, regardless of patients receiving other anticancer treatment.

Phase 1 portion: In Phase 1, there will be 3 cohorts of approximately 7 patients each; patients may have either CP or AP CML. All patients will be given a fixed dose of 2.5 mg omacetaxine subcutaneous injection twice daily. Every effort will be made to include an equal number of patients in each BSA cohort. Cohort 1 will include patients whose BSA is less than 1.7 m^2. Cohort 2 will include patients with a BSA between 1.7 m^2 to 2.0 m^2 inclusive. Cohort 3 will include patients with BSA greater than 2.0 m^2. Based on data from previous clinical research studies, the range of BSA for patients enrolled in those studies was 1.39 to 2.46 m^2 for CP patients, and 1.34 to 2.31 m^2 for AP patients (data on file). Because it is known that women usually have a smaller BSA than men, all efforts must be made to include at least 2 men in cohort 1 to reduce possible gender bias. After cycle 1, patients will continue to receive omacetaxine for 12 months until intolerance or disease progression while safety and efficacy parameters are followed.

Phase 2 portion: Following the analysis of pharmacokinetic and preliminary safety and efficacy data from the patients in Phase 1, a decision whether or not to continue to Phase 2 will be made. If the Phase 1 data indicate that a fixed-dose regimen is not appropriate for subcutaneously administered omacetaxine, enrollment into the Phase 2 portion will be stopped and the study will be terminated. It is anticipated that the analysis of pharmacokinetic and preliminary safety and efficacy data from the patients in Phase 1 will take approximately 2 months. Assuming a fixed-dose regimen is considered appropriate on the basis of the Phase 1 data, a total of up to 45 patients with CP CML and a total of up to 67 patients with AP CML will be enrolled in Phase 2.

Phase 1 and Phase 2: Omacetaxine will be administered by subcutaneous injection twice daily. For cycle 1, the first dose will be administered at the investigational center. Subsequent doses (in prefilled syringes) may be administered on an outpatient basis after training takes place. See Section 5.1.1 regarding training for the patient or caregiver for administration of omacetaxine.

Patients will be evaluated every 7 days with complete blood and platelet counts up to and including cycle 5, and every 2 weeks (±2 days) after cycle 5 (see Section 3.11.2.5); the number

of consecutive doses of omacetaxine or intervals between subsequent cycles may be adjusted, as clinically indicated, according to guidelines provided in Section 5.1.2.

The following tests will be performed every 3 months (ie, every 3 cycles) while on study, for all patients:

- bone marrow aspiration and cytogenetics every 3 months
  If patients show other clinical signs of disease progression they may not need to undergo a bone marrow evaluation. The treatment cycle following a bone marrow procedure for the long-term responders may begin up to 7 (±3) days after the bone marrow procedure. Cytogenetic response evaluation will be based on standard cytogenetic analysis (at least 20 metaphases are to be analyzed).
  Note: After a patient achieves a confirmed cytogenetic response, bone marrow aspiration with cytogenetics will be performed every 12 months or as often as clinically indicated. At this stage, after the patient has been on study for at least 12 months, chromosome banding analysis of marrow cell metaphases (with at least 20 metaphases analyzed) can be substituted by florescence in situ hybridization (FISH) on blood cells once a complete cytogenetic response has been confirmed (Baccarani et al 2013, SYNRIBO prescribing information).

- measure BCR-ABL transcript levels by real-time, quantitative polymerase chain reaction (PCR) of peripheral blood performed locally
  Note: After a patient achieves a confirmed complete cytogenetic response, RT-PCR BCR-ABL testing should be performed every 6 months unless clinically indicated to do it more often (Appendix A).

- quantitative BCR-ABL kinase domain mutation analysis of peripheral blood sample (Appendix B) prior to omacetaxine treatment cycle (performed locally)
  However, this may omitted if the patient did not have any clinical sign of failure to treatment, or did not show any clinical signs of progression.

- electrocardiogram (ECG)

For patient convenience, these studies may be scheduled to be obtained prior to the next scheduled omacetaxine treatment cycle.

Note: Any or all of the above procedures may be conducted earlier than a scheduled 3-month interval if clinically indicated, eg, a rising level of BCR-ABL transcript is observed.

Patients not demonstrating evidence of clinical response after 6 cycles will be considered for removal from the study; however, with permission of the sponsor's medical monitor, treatment may continue, if clinically indicated, provided there is no evidence of toxicity grade 3 or above.

In patients achieving a CHR or major cytogenetic response (either complete, or partial cytogenetic response, up to 35% Ph+ metaphases) (Appendix A) , the response will be confirmed by a repeat complete blood count (CBC), bone marrow aspiration (for patients with a hematologic response), cytogenetics of the bone marrow aspirate (for patients with a cytogenetic

response), and BCR-ABL transcript levels by quantitative reverse transcription-polymerase chain reaction (RT-PCR) of peripheral blood, at the intervals specified below. For patient convenience, confirmatory studies may be scheduled to be done prior to the next scheduled omacetaxine treatment cycle (rather than exactly at 4 or 8 weeks after the initial response, as specified below).

- chronic phase CML: **Confirm** the response at least 8 weeks after the initial documentation of the response, ie, at least 8 weeks after the patient first meets the clinical and laboratory criteria for a response, as defined in Appendix A.

- accelerated phase CML: **Confirm** the response at least 4 weeks after the initial documentation of the response, ie, at least 4 weeks after the patient first meets the clinical and laboratory criteria for a response, as defined in Appendix A.

If the CBC, bone marrow aspiration, and/or cytogenetic results do not confirm the clinical response and the patient is already on maintenance treatment cycles, the patient may continue on maintenance therapy or may revert back to induction cycles (ie, 14 days of omacetaxine treatment) or the highest number of days tolerated previously, if clinically indicated.

Patients who demonstrate CHR, hematologic improvement (HI), or any cytogenetic response, as defined in Appendix A, may convert from induction to maintenance therapy (see Section 5.1, Treatment Plan).

3.2. Primary and Secondary Measures and Endpoints

3.2.1. Primary Efficacy Measures and Endpoints

The primary efficacy variable for patients with CP CML is the proportion of patients who achieve a major cytogenetic response (MCyR: complete cytogenetic response with no Ph+ metaphases and partial cytogenetic response with 1 to 35% Ph+ metaphases)

The primary efficacy variable for patients with AP CML is the proportion of patients who achieve a major hematologic response (MaHR: complete hematologic response or no evidence of leukemia) and/or MCyR.

See Appendix A for the measures for response. See Table 2 for the endpoints for response.

3.2.2. Secondary Efficacy Measures and Endpoints

The secondary efficacy measures and endpoints are as follows:

- duration of response, defined for responders as the time interval from the first reported date of MCyR or MaHR, as defined above, to the earliest date of objective evidence of disease progression (ie, development of accelerated-phase CML), relapse (ie, loss of complete hematologic or major cytogenetic response), or death

- molecular response by site (peripheral transcript of BCR-ABL) (Appendix B) assessed every 3 months (ie, every 3 cycles)

- progression-free survival, defined as the time interval from date of first dose to earliest date of objective evidence of disease progression (ie, development of accelerated-phase CML), relapse (ie, loss of complete hematologic or major cytogenetic response), or death

- overall survival, defined as the time interval from date of first dose to date of death from any cause

3.2.3. Safety Measures and Endpoints

The safety and tolerability of omacetaxine treatment will be assessed throughout the study by evaluating the following safety variables:

- adverse events (type, frequency, severity, and causality)

- clinical laboratory test results (serum chemistry and hematology) at various points in the study

- exploratory predictors of toxicity such as myelosuppression to assist with safety signals

- vital signs measurements (blood pressure, heart rate, respiratory rate, body temperature)

- physical examination (including weight)

- 12-lead ECG

- concomitant medication usage

3.2.4. Pharmacokinetic Measures and Endpoints

See Section 8.1 for pharmacokinetic measures and endpoints.

3.3. Randomization and Blinding

This is a nonrandomized, open-label study.

3.4. Study Drugs and Dosage

3.4.1. Investigational Product and Dosage

The investigational drug for this study is omacetaxine mepesuccinate. Omacetaxine drug product is a lyophilized vial containing 3.5 mg omacetaxine and 10 mg mannitol in an 8-mL clear glass vial, sealed with rubber stopper and aluminum flip-off seal. Investigational centers will be given vials of 3.5 mg omacetaxine. Omacetaxine will be reconstituted by a healthcare professional.

Omacetaxine will be administered by subcutaneous injection at a fixed dose of 2.5 mg twice daily for 7 or 14 consecutive days every 28 days, over a 28-day cycle. The first dose of the day for cycle 1 will be administered at the investigational center. Subsequent doses (in prefilled syringes) may be administered on an outpatient basis after training takes place, and recorded and verified in the patient diary, unless the patient must come back to obtain more drug or perform test procedures, including pharmacokinetics.

A more detailed description of administration procedures is provided in Section 5.1.

3.4.2. Other Study Drugs and Dosage

This is an uncontrolled study with no other study drug.

3.5. Duration of Patient Participation

The study will consist of up to a 7-day screening period, and treatment for up to 12 months depending on response and tolerability. Patients will also have an end-of-treatment follow-up visit approximately 28 days (+2 days) after the last dose of omacetaxine. Patients will be monitored for progression and survival for at least 1 year after the last treatment dose of omacetaxine, death, or lost to follow-up, whichever comes first, regardless of patients receiving other anticancer treatment.

3.6. Stopping Rules and Discontinuation Criteria

During the conduct of the study, serious adverse events will be reviewed (see Section 7.1) as they are reported from the investigational center to identify safety concerns along with reviewing the adverse events collected and monitored from the clinical investigational centers. The study may be terminated by the sponsor at any time.

A review of all pharmacokinetic and preliminary safety and efficacy data will be performed after the last patient completes 1 cycle of treatment and undergoes pharmacokinetic sample collection in the Phase 1 portion of the study. This review will determine whether it is appropriate to further evaluate the fixed-dose regimen or a modified fixed-dose regimen in the Phase 2 portion of the study, or terminate the study.

Safety and efficacy will be reviewed by an independent DMC. The DMC will also review the pharmacokinetic analysis from Phase 1. See Section 7 for further information.

A patient may discontinue participation in the study at any time for any reason (eg, lack of efficacy, consent withdrawal, adverse event). The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, protocol violation or deviation as defined in Section 11.1.2, noncompliance, adverse event).

3.7. Study Drug Supply and Accountability

An Interactive Response Technology (IRT) system will be used to manage the omacetaxine supply at the investigational center and/or central pharmacy. The information regarding the vendor will be provided in the project plan.

Omacetaxine will be provided to the principal investigators by the distributer after authorization from the sponsor.

Investigational centers will be given vials of 3.5 mg omacetaxine. Saline, syringes, needles that are needed may be supplied or reimbursed by sponsor. Spill kits, and written instructions, will be provided by the sponsor.

A training pamphlet for the subcutaneous administration of omacetaxine, for handling spills of omacetaxine (if they were to occur after reconstitution), for accurate record keeping of administered omacetaxine (ie, patient diaries), instructions on how to record data on patient diaries, handling, storage, disposal, and shipping of reconstituted omacetaxine will also be provided to the study staff and patient. For more details, refer to the Pharmacy Manual.

3.7.1. Study Drug Storage and Security

The vials of lyophilized powder (3.5 mg per vial) must be kept in their original package, protected from light, at controlled room temperature (20°C to 25°C with excursions to 15°C to 30°C), in a cabinet or other enclosure, which is securely locked. Access should be restricted to the principal investigator, investigational pharmacist, or other authorized designee at each investigational center. Neither the principal investigator nor any designees may provide the investigational drug to any study patient not participating in this protocol. Use omacetaxine immediately after reconstitution, or, if not possible, within the timelines provided in Table 1. Do not reuse. Updated stability information will be provided in the Pharmacy Manual and also as notification to the sites in the event of updates to this information.

Table 1: Time to Administration After Reconstitution

Storage conditions	Time to administration
Room temperature (20°C to 25°C [68°F to 77°F])	Within 12 hours of reconstitution
Refrigerated (2°C to 8°C [36°F to 46°F])	Within 6 days (144 hours) of reconstitution

3.7.2. Study Drug Accountability

Each study drug shipment will include a packing slip, listing the contents of the shipment, and drug return instructions and any applicable forms.

The investigator is responsible for ensuring that deliveries of study drug and other study materials from the sponsor are correctly received and recorded, handled and stored safely and

properly in accordance with the CFR or local regulations, and used in accordance with this protocol.

A record of study drug accountability (ie, study drug and other materials received, used, unused, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused study drug will be disposed of, or returned to the sponsor or its designee.

For the first cycle, the first dose will be reconstituted by the healthcare professional and administered at the investigational center. For any additional cycles, the first dose may be administered at the investigational center by a healthcare professional, self-administered at home by the patient, or administered by the Sponsor selected home care agency professional at the home of the patient. Except for cycle 1 of Phase 1 (see Table 3 and Table 4 for the different dosing schedules), the second dose of day 1 may be dispensed to the patient by the study doctor/pharmacist/trained study personnel or central pharmacy in a syringe filled with the correct volume of omacetaxine (fixed dose). This will be repeated every day for 14 days or 7 days of treatment, for induction or maintenance cycles, respectively (or according to dose delay and modifications). Additionally, accurate record keeping of all reconstituted fixed doses of omacetaxine administered bid per cycle will be required from the investigational center and the patient via the patient diaries and medical source documents. Dosing information from the diaries will be entered into a database at approximately weekly visits, unless otherwise noted, during dosing periods, and verified by study staff or designee. Patients and investigational centers will be provided with instructions on how to complete the patient diaries, and will be required to make them available to verify dosing. Patients will also be instructed to bring their diary to the clinic at each visit so that the study staff can review it and provide re-training, if needed.

Drug Accountability Logs will indicate patient identifying information, as well as the date and quantity of study drug received and dispensed by the investigational center pharmacy or central pharmacy, expiration of the reconstituted solution, as well as study drug returned to the sponsor. These records will be reviewed by the sponsor. The sponsor may supply the Drug Accountability Logs to facilitate this inventory control or the principal investigator may use forms authorized by the investigational center pharmacy or central pharmacy, providing the institution's forms capture all inventory and dispensing data required by the sponsor. When the study is terminated, the principal investigator or his/her designees will provide a copy of the completed drug accountability records to the sponsor.

All prepared syringes of study drug (fixed dose) and other needed supplies (biohazard container, spill kits, etc) will be dispensed from the investigational center pharmacy or central pharmacy under the direct supervision of study staff and in accordance with the investigational center’s standard operating procedures (SOPs). Drug logs will be used to ensure compliance. In general, unless otherwise noted with written rationale (ie, reimbursement), the patient will be provided with a biohazard container and spill kit with written instructions by the sponsor in order to return used syringes as instructed and trained. The patient will be instructed on how to return the used syringe syringes and used supplies as recorded in the training materials. To ensure compliance of the reconstituted doses of omacetaxine and required procedures, outpatient nursing services may

also be available, as needed, by the sponsor, or reimbursed by the sponsor, depending on where the patient lives.

Special handling and disposal procedures should be followed according to applicable guidelines issued for hazardous drugs, training materials, and training received. Patients will be instructed and trained with training materials provided by the sponsor, not to place used needles, syringes, or vials in household trash or recycle.

For more details regarding training materials and above information, please refer to the Pharmacy Manual.

3.8. Maintenance of Randomization and Blinding

This is an open-label study with no blinding.

3.9. Source Data Recorded on the Case Report Form

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed onto the case report form (CRF). Data may not be recorded directly onto the CRF and considered as source data unless the investigational center obtains written documentation from the sponsor, before the beginning of the study, indicating which data are permitted to be recorded directly onto the CRF. Source documents, including test results and/or assessments (eg, clinical laboratory test results, ECG data and assessments, efficacy measurements) collected or performed by institutions outside of the investigational center, are retained by the investigational center (see Section 13.3.1). The CRFs are filed in the sponsor's central file.

The principal investigator or his designee(s) will maintain progress notes in the institution's medical records to document all significant observations through the course of each patient's study participation. At a minimum, these notes should contain:

- documentation of written informed consent, medical history, and current physical condition of patient to verify protocol entry criteria at screening
- the dates of all study-related visits, study number, patient number, and drug being evaluated
- general patient status remarks, including any significant medical findings; the severity, frequency, and duration of any adverse events or abnormal laboratory findings, and the principal investigator's assessment of whether or not they are study drug-related must also be recorded
- any changes in concomitant medications or dosages (including start and stop dates)
- any dosing changes, interruptions or discontinuation in study medication and review of completed patient diaries

- a specific reference to the procedures completed at each study-related visit
- the signature or initials of all persons making an entry in the progress notes
- the date of study completion or termination with assessment of patient's overall condition

In addition, any contact with the patient via telephone or other means that provides significant clinical information will also be documented in the progress notes, as described above.

Any changes to information in the study progress notes, other source documents or the case report forms will be made by drawing a single line through the incorrect entry, initialing and dating on the day the change is made by study personnel authorized to make the change. The revised information should be entered adjacent to the corrected entry. Incorrect data must not be obliterated by any means, including by correction fluid.

Study participants must not be identified by name on any study documents. Patients will be identified by initials and assigned patient numbers only. The principal investigator will allow the sponsor or its representative, or an appropriate representative of the competent authorities to inspect study documents (eg, consent forms, patient diaries, drug distribution forms, IRB approval) and pertinent hospital or clinic records for confirmation of data throughout the study period.

3.10. Time Schedule

The study is expected to start enrolling in approximately the second quarter of 2014 and be completed enrollment approximately in 2016. The study is planned to be conducted at approximately 24 study centers in North America, Europe, and Asia.

3.11. Study Procedures

Study procedures and assessments with their timing are summarized in Table 2, Table 3, and Table 4.

Table 2: Study Procedures and Assessments

Procedures and assessments	Screening[a]	Omacetaxine induction or maintenance treatment 28-day cycles (±1 day)(up to 12 cycles total)						Study completion or early termination[b]	Follow-up[c]
		Day 1 induction cycles	Day 1 maintenance cycles	Cycles 1 to 5 (days 7, 14, 21)	Cycle 6 to end of treatment day 14	Every 3 months on study[d]	Confirmation of response[e]		
Informed consent	X								
Inclusion/Exclusion criteria	X								
Medical history	X								
Urine or serum pregnancy test	X[f]								
Physical exam	X	X[g]	X[g]					X	
Prior medications	X								
Height	X								
Weight	X	X[g]	X[g]					X	
Calculate body surface area[h]	X	X	X						
Vital Signs (HR, RR, BP, T)	X	X[i]	X[i]					X	
Chest x-ray	X[j]								
ECG	X[j]	X[k]		X[l]		X		X	
Hematology[m]	X	X[g]	X[g]	X[n]	X[o]		X	X	
Serum chemistry[p]	X	X[g]	X[g]	X[n]	X[o]			X	
Bone marrow aspiration and cytogenetics[q]	X[j]					X[r]	X[s]	X[q]	
BCR-ABL quantitative transcript levels by PCR[t]	X					X[r]	X	X	
BCR-ABL mutation analysis	X[u]					X[rv]			
Urinalysis	X								

Table 2: Study Procedures and Assessments (Continued)

Procedures and assessments	Screening[a]	Omacetaxine induction or maintenance treatment 28-day cycles (±1 day)(up to 12 cycles total)						Study completion or early termination[b]	Follow-up[c]
		Day 1 induction cycles	Day 1 maintenance cycles	Cycles 1 to 5 (days 7, 14, 21)	Cycle 6 to end of treatment day 14	Every 3 months on study[d]	Confirmation of response[e]		
Document other measures of disease and disease symptoms	X	X	X					X	
ECOG performance status	X	X[g]	X[g]					X	
Patient diary review		X[w]	X	X	X	X		X	
Drug accountability		X[w]	X	X	X	X		X	
Concomitant medication		X	X	X	X	X	X	X	
Adverse event inquiry		X	X	X	X	X	X	X	
Omacetaxine dosing		Days 1 through 14 during induction[u] and days 1 through 7 during maintenance							
Survival[x]		X	X	X	X	X	X		X
Other anticancer treatment									X

[a] Screening period is 7 days before first dose of study drug except for bone marrow aspiration, cytogenetics, ECG, and chest x-ray, which may be performed within 30 days before start of study drug.

[c] Follow-up visits every 3 months (±7 days); the first visit will be in person but the rest may be by telephone contact. Follow-up will continue until patient's death, is lost to follow-up, or until 12 months after the last treatment cycle, whichever occurs first, regardless of receiving other anticancer treatment. Follow-up is required even if a patient is withdrawn from treatment with omacetaxine.

[d] For patient convenience, these studies may be scheduled to be obtained prior to the next scheduled omacetaxine treatment cycle. Additional studies may be conducted earlier than a scheduled 3-month interval if clinically indicated, eg, a rising level of BCR-ABL transcript is observed.

[e] For patients with chronic phase CML, confirm the response at least 8 weeks after the patient first meets the clinical and laboratory criteria for a response. For patients with accelerated phase CML, confirm the response at least 4 weeks after the patient first meets the clinical and laboratory criteria for a response. For patient convenience, confirmatory studies may be scheduled to be done prior to the next scheduled omacetaxine treatment cycle (rather than exactly at 4 or 8 weeks after the initial response).

[b] If a patient completes treatment with omacetaxine or is withdrawn from treatment, assessments will be performed at an end-of-treatment visit 28 days (+2 days) after the last dose of study drug. If the patient is withdrawn from treatment, an end-of-treatment visit may occur before 28 days after the last dose of omacetaxine to allow the patient to enter follow-up.

[f] For women of childbearing potential. Repeat as clinically indicated.

[g] On the day of or within 3 days prior to start of the treatment cycle. Review results prior to initiating a treatment cycle.
[h] Body surface area will be calculated during cycles 1 through 3 of study drug treatment.
[i] Measure vital signs (HR, BP, RR, T) within 30 minutes prior to administration of omacetaxine and 20 minutes post-dose (±5 min) on day 1 of each treatment cycle. If the patient has hypotension (systolic blood pressure <90 mm Hg), vital signs should be taken and recorded more frequently, until the patient has stabilized. (In the case of outpatient injections, sometimes points may be omitted if logistically not possible, eg, the time point occurs over the weekend.)
[j] Chest x-ray may be omitted if a prior study, such as a CT of the chest, is completed within 30 days of first dose of omacetaxine. A screening bone marrow or ECG is required only if a prior one has not been performed within 30 days of first dose of omacetaxine.
[k] Prior to the first 3 cycles (cycles 1 through 3) whether induction or maintenance. It may be omitted at cycle 1 if one was done within 30 days prior to the first dose of omacetaxine on day 1 of cycle 1). In other countries, ECGs may be done before and after every omacetaxine cycle, or as directed.
[l] Electrocardiogram after completion of day 14 of treatment, induction cycle 1, if the patient is available for this exam.
[m] Complete blood counts (±2 days) to include hematocrit, hemoglobin, RBC, WBC, differential, platelet count.
[n] During cycles 1 through 5 serum chem 7 (sodium, chloride, CO_2 content, creatinine, BUN or urea, glucose, and potassium) will be performed on days 7 (±2), 14 (±2), and 21 (±2). Studies may be obtained at a local laboratory, with results transmitted to the study investigational center in a timely manner as they become available.
[o] Full serum chemistry and hematology to be performed every 2 weeks (±2 days) after cycle 5.
[p] Full serum chemistry to be performed at screening and after cycle 5. During cycles 1 through 5, chem 7 (sodium, chloride, CO_2 content, creatinine, BUN or urea, glucose, and potassium) is to be performed.
[q] Bone marrow exam with cytogenetic analysis to be performed by the G-banding technique. Marrow specimens will be examined on direct short-term (24-hour) cultures; at least 20 metaphases are to be analyzed. May be omitted at screening if bone marrow and cytogenetic analysis have been done in the preceding 30 days and the patient had not received antileukemic therapy during this period (other than palliative therapy, eg, hydroxyurea). After 12 months on study, and once a complete cytogenetic response has been confirmed, may substitute chromosome banding analysis with FISH on blood cells.
[r] For the convenience of all patients, these studies may be scheduled prior to the next scheduled omacetaxine treatment cycle. Additional studies may be conducted earlier than a scheduled 3-month interval if clinically indicated, eg, a rising level of BCR-ABL transcript is observed.
[s] Obtain bone marrow cytogenetic study to confirm a cytogenetic response.
[t] Obtain BCR-ABL quantitative transcript levels by quantitative PCR analysis of peripheral blood. BCR-ABL transcripts will be detected by real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis on peripheral blood. After a patient achieves a confirmed complete cytogenetic response, this test should be performed every 6 months unless clinically indicated to do it more often.
[u] May be omitted if performed within 14 days before the first dose of omacetaxine.
[v] During the study it is only requested if the patient failed to respond or progressed.
[w] Except for day 1 of cycle 1 of induction.
[x] Obtain survival and progression-free survival defined as the time interval from date of first dose to date of death from any cause, or 12 months after last treatment cycle whichever occurs first. The patient is requested to be monitored even if the patient is withdrawn from the planned omacetaxine treatment or received other anticancer treatment.

HR=heart rate; RR=respiratory rate; BP=blood pressure; T=temperature; RBC=red blood cell; WBC=white blood cell; BUN=blood urea nitrogen; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; PCR=polymerase chain reaction; CML=chronic myeloid leukemia, CO_2=carbon dioxide, FISH=florescence in situ hybridization.

Table 3: Pharmacokinetic Sampling Schedule, Phase 1, Cycle 1 Induction, Days 1 Through 17

Day	Omacetaxine dose per day[a]	Times for blood plasma draws
1	Dose 1	–20 min, 15 (±5 min), 30 (±5 min), and 45 (±5 min) minutes and, 1 hr (±5 min), 2 hr (±10 min), 4 hr (±10 min), 8 to 12 hr (±15 min)
	No Dose 2	NA
2	No Dose 1	24 hr (±1 hr)
	No Dose 2	NA
3	No Dose 1	48 hr (±1 hr)
	No Dose 2	NA
4	Dose 1	72 hr (±1 hr) (prior to dose 1 on day 4)
	Dose 2	NA
5-9	Dose 1 and Dose 2	NA
10 or 11 or 12[b]	Dose 1	Predose <1 hr after dose 1 1 to 12 hr after dose 1
	Dose 2	NA
13 or 14 or 15 or 16 or 17[c]	Dose 1 and Dose 2	Either predose 1 or predose 2

[a] To accommodate the pharmacokinetic objective of the study, during cycle 1, 1 dose is given in the morning of day 1, no dose 2 on day 1, no doses are given on day 2 or day 3.
[b] Pharmacokinetic samples to be drawn once, either on day 10 or 11 or 12. Day 10 or 11 or 12, <1 hr sample and 1-12 hr sample should be drawn at least 30 minutes apart.
[c] Pharmacokinetic samples to be drawn once, either on day 13, or 14, or 15, or 16 or 17.
min=minutes; hr=hour; NA=not applicable.
Note: Exact volume of drug injected, actual time of dosing, and sample collection time will be recorded.

Table 4: Pharmacokinetic Sampling Schedule, Phase 1 (Cycles 2 and 3) and Phase 2 (Cycles 1, 2, and 3)

Cycle 1, 2, 3	Omacetaxine dose	Times for blood plasma draws
Day 1[a]	Dose 1 Dose 2	<1 hr after dose 1 1 to 12 hr after dose 1 NA
After day 1 during week 1[b]	Dose 1 and Dose 2	One sample either predose 1 or predose 2
Any day during week 2[b]	Dose 1 and Dose 2	One sample either predose 1 or predose 2

[a] Phase 2 only for cycles 1 to 3, and Phase 1 for cycles 2 and 3. The dosing is as prescribed either 14 days bid or 7 days bid if in maintenance, or as per the investigator if the patients had dose delays or reductions after cycle 1. Exact volume injected of drug, actual time of dosing and sample collection will be recorded.
[b] Day 10 or 11 or 12, <1 hr sample and 1-12 hr sample should be drawn at least 30 minutes apart.
bid=twice daily; hr=hour; NA=not applicable.

3.11.1. Procedures for Screening and Enrollment

A signed and dated informed consent form will be obtained before screening procedures commence. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the protocol-specific evaluations. In addition, disease-specific assessments performed within a specified time frame before informed consent may be used for the study. Patients will acknowledge and agree to the possible use of this information for the study by giving informed consent.

After informed consent is obtained, patients who are screened will be assigned an 8-digit permanent identification number such that all patients from each investigational center are given consecutive identification numbers in successive order of inclusion. The first 2 digits of the screening number will be the number assigned to the country where the investigational center is located, the next 3 digits will be the designated investigator center number, and the last 3 digits will be assigned at the investigator center (eg, if the number assigned to the country is 01, the 3rd patient screened at center 5 would be given the number of 01005003).

During the enrolment period of the study, once the investigator has confirmed that the patient meets all eligibility criteria and has obtained patient informed consent, the investigational center staff must first register the patient with the sponsor or its designee, in order to enroll the patient in the study. Study reference materials for the patient registration procedure will be provided separately to each study center upon initiation of the study. Confirmation of patient enrollment will be sent to the investigator following receipt and review of the registration.

A patient who is screened but not enrolled, eg, because entry criteria were not met or enrollment did not occur within the specified time, may be considered for screening again if, eg, there is a change in the patient's medical background or a modification of study entry criteria. Consultation with the sponsor or designee must occur first. The patient will sign a new informed consent and a new patient number will be assigned.

The following activities and evaluations will be performed up to 7 days prior to administration of the first dose of study drug, unless otherwise specified, in order to determine if a patient meets the eligibility criteria:

- written informed consent (must be obtained prior to screening evaluations)
- review inclusion/exclusion criteria
- review medical history
- review medication history
- perform physical examination
- measure height and weight and calculate body surface area
- perform vital signs measurements (temperature, heart rate, respiratory rate, systolic and diastolic blood pressures)

- perform clinical laboratory tests, as follows:
  - hematology
  - full serum chemistry
  - urinalysis
  - bone marrow aspiration and cytogenetics, if not performed within 30 days before the first dose of omacetaxine
  - pregnancy test (urine or serum) for women of childbearing potential
  - determination of the types of BCR-ABL transcripts and BCR-ABL transcript peripheral blood levels by quantitative reverse transcription PCR (PCR) locally performed (Appendix B)
  - quantitative BCR-ABL kinase domain mutation analysis of peripheral blood sample locally performed if not available within 14 days before first dose of omacetaxine (Appendix B)
- documentation of all other measures of disease and disease symptoms (eg, extramedullary disease)
- ECG, unless one was performed within the preceding 30 days. Prior to study entry, any other ECG abnormalities noted at screening other than myocardial infarction within the previous 12 weeks and felt by the investigator not to be medically relevant, must be documented as such.
- chest x-ray unless one was performed within the preceding 30 days
- ECOG performance status (Appendix C)

3.11.2. Procedures During Study Drug Treatment (Induction and Maintenance)

In addition to the procedures specified in this section, data obtained from any unscheduled procedures and during any unscheduled visits will be collected on the appropriate CRF.

3.11.2.1. Procedures for Day 1 of Each Treatment Cycle

The following assessments will be performed on day 1, or within 3 days before day 1 of each treatment cycle, unless otherwise specified:

- physical examination (for cycle 1 may be omitted if done at screening within 7 days of dosing)
- weight at each cycle (height at screening)

- collect calculated BSA from investigational center (cycle 1 to cycle 3 only)
- ECG prior to cycles 1 through 3 only (for cycle 1, it may be omitted if one was done within 30 days prior to the first dose of omacetaxine on day 1 of cycle 1)
- vital signs (temperature, heart rate, respiratory rate, systolic and diastolic blood pressure) within 30 minutes before omacetaxine and 20 minutes post-injection (±5 min) on day 1 of each treatment cycle
  Note: If the patient has hypotension (systolic blood pressure <90 mm Hg), vital signs should be taken and recorded more frequently, until the patient has stabilized. If no significant variations are observed during the first cycle, vital signs will be checked preceding each new treatment cycle.
- ECOG performance status
- hematology (Appendix D)
- serum chemistry 7 (sodium, chloride, carbon dioxide [CO_2] content, creatinine, blood urea nitrogen (BUN) or urea, blood glucose, and potassium only) (Appendix D)
- documentation of all other measures of disease and disease symptoms
- drug accountability including review of completed patient diaries (except for day 1 when the dose will be recorded at the investigational center)
- adverse event inquiry
- concomitant medication inquiry
- Review of updated patient diaries and inquiries on compliance of omacetaxine administration. Please refer to the Patient Instructions on Subcutaneous Injection and Diary Completion for further details.

3.11.2.2. Pharmacokinetic Procedures, Phase 1, Cycle 1 Only

Blood sampling for pharmacokinetic analysis will be obtained from all patients in Phase 1 during cycle 1 of induction, as follows (see Table 3):

- On days 1 through 4 as follows:
  - 20 minutes prior to, 15 (±5 min), 30 (±5 min), and 45(±5 min) minutes and 1 (±5 min), 2 (±10 min), 4 (±10 min), 8 to 12 (±15 min), 24 (±1 hr), 48 (±1 hr), and 72 (±1 hr) hours (predose 1 on day 4) after administration of the first dose of omacetaxine
- On day 10 or 11 or 12, as follows:

- predose, within (<) 1 hour after dose 1, and 1 to 12 hours after dose 1
- <1 hr sample and 1-12 hr sample should be drawn at least 30 minutes apart.

- One sample on day 13, 14, 15, 16, or 17 as follows:
  - either predose 1 or predose 2

3.11.2.3. Pharmacokinetic Procedures, Phase 1, Cycles 2 and 3 and Phase 2, Cycles 1 Through 3

Blood samples (2.5 mL) will be obtained in Phase 1 on day 1 of cycles 2 and 3 as follows (see Table 4):

- within (<) 1 hour after dose 1
- 1 to 12 hours after dose 1
- 1 sample either predose 1 or predose 2 on any day after day 1 during week 1
- 1 sample either predose 1 or predose 2 on any day during week 2

Blood samples (2.5 mL) will be obtained in Phase 2 on day 1 of cycles 1, 2 and 3 as follows (see Table 4):

- within (<) 1 hour after dose 1
- 1 to 12 hours after dose 1
- 1 sample either predose 1 or predose 2 on any day after day 1 during week 1
- 1 sample either predose 1 or predose 2 on any day during week 2

On Day 10 or 11 or 12, the <1 hr sample and 1-12 hr sample should be drawn at least 30 minutes apart.

3.11.2.4. Procedures During Cycles 1 Through 5 of Treatment (Days 7 [±2], 14 [±2], 21 [±2])

The following assessments will be performed on days 7±2, 14±2, and 21±2 of the first 5 cycles of treatment, unless otherwise specified:

- hematology
- serum chemistry 7 (sodium, chloride, CO_2 content, creatinine, BUN or urea, blood glucose, and potassium only)
- ECG (after completion of day 14 of treatment in cycle 1, if the patient is available)

- adverse event inquiry
- concomitant medication inquiry
- drug accountability including review of completed patient diaries

Tests may be obtained at a local laboratory, with results transmitted to the study investigational center in a timely manner (especially if needed before administration of omacetaxine or to follow-up an adverse event).

3.11.2.5. Procedures After Cycle 5 of Treatment

The following assessments will be performed on day 14 (±2 days) (versus weekly) for all treatment cycles after cycle 5.

- hematology
- full serum chemistry (Appendix D)
- adverse event inquiry
- concomitant medication inquiry
- review of updated patient diaries and inquiries on compliance of omacetaxine administration

3.11.2.6. Procedures During Study Drug Treatment–Every 3 Months (ie, every 3 cycles) on Study–All Patients

The following studies will be obtained every 3 months (ie, every 3 cycles) while on study, in all patients, unless otherwise specified:

- bone marrow aspiration and cytogenetics every 3 months
  Performance of bone marrow procedures for these patients should be based on the need to demonstrate continued cytogenetic response and clinical circumstances (ie, may not be needed if clinical disease progression is documented). Cytogenetic response evaluation will be based on standard cytogenetic analysis (at least 20 metaphases are to be analyzed).
- measure BCR-ABL transcript levels by real-time, PCR of peripheral blood
- quantitative BCR-ABL kinase domain mutation analysis of peripheral blood sample, locally performed, if a patient failed to respond or progressed after treatment with omacetaxine (follow-up of BCR-ABL mutations) (Appendix B)
- ECG (may be performed more frequently as clinically indicated or as required by standard of care in a particular country)

- drug accountability
- adverse event inquiry
- concomitant medication inquiry
- review of updated patient diaries and inquiries on compliance of omacetaxine administration

For patient convenience, these studies may be scheduled to be obtained prior to the next scheduled omacetaxine treatment cycle.

Note: Any or all of the above studies may be conducted earlier than a scheduled 3-month interval if clinically indicated, eg, a rising level of BCR-ABL transcript is observed.

3.11.2.7. Confirmation of Complete Hematologic Response or Major or Complete Cytogenetic Response (Induction or Maintenance)

In patients achieving a CHR or major cytogenetic response (either complete or partial cytogenetic response, up to 35% Ph+ metaphases) during the induction phase, the response will 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 cytogenetic response), and BCR-ABL transcript levels by quantitative reverse transcription-polymerase chain reaction (RT-PCR) of peripheral blood, at the intervals specified below. For patient convenience, confirmatory studies may 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).

- chronic phase CML: Confirm the response at least 8 weeks after the initial documentation of the response, ie, at least 8 weeks after the patient first meets the clinical and laboratory criteria for a response, as defined in Appendix A.
- accelerated phase CML: Confirm the response at least 4 weeks after the initial documentation of the response, ie, at least 4 weeks after the patient first meets the clinical and laboratory criteria for a response, as defined in Appendix A.

If the CBC, bone marrow aspiration, and/or cytogenetic results do not confirm the clinical response and the patient is already on maintenance treatment cycles, the patient may revert back to induction cycles (ie, 14 days omacetaxine treatment) or the highest dose tolerated previously, if clinically indicated.

3.11.3. Procedures After Study Drug Treatment

3.11.3.1. End-of-Treatment Visit

The following procedures will be performed at the end-of-treatment visit, 28 days (+2 days) after the last dose of study drug, unless otherwise specified:

- physical examination
- weight
- vital signs (temperature, heart rate, respiratory rate, systolic and diastolic blood pressure)
- laboratory studies (Appendix D)
  - hematology
  - serum chemistry
- bone marrow aspiration (or biopsy) if indicated ± cytogenetics (for confirmation of response)
- ECG
- BCR-ABL transcript levels by quantitative PCR of peripheral blood at local laboratory (Appendix B)
- other measures of disease and disease symptoms, eg, extramedullary disease
- ECOG performance status
- drug accountability including review of completed patient diaries
- adverse event inquiry
- concomitant medication inquiry

For patients who complete the study, or for those who withdraw prematurely from the study, final evaluations will be performed 28 days (+2 days) after the last dose of study drug. Patients who withdraw prematurely may have their end-of-treatment visit earlier than 28 days after the last dose of omacetaxine. Patients with ongoing adverse events or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in Section 7.1.2 and Section 7.3, respectively.

If a patient withdraws from the study during the treatment period, the reason must be determined and recorded on the patient's CRF (see Section 4.3). Patients who withdraw prematurely from treatment with omacetaxine (planned period of up to 12 cycles) are still required to enter the follow-up period unless they withdraw consent. For patients who withdraw consent, every attempt will be made to determine the reason.

3.11.3.2. Follow-up

Patients will be monitored every 3 months (±7 days) for progression (if the patient had not progressed at the time of the end-of-treatment visit) and survival for 1 year after the last dose of

omacetaxine, death, or lost to follow-up, whichever comes first, regardless of patients receiving other anticancer treatment. If the patient is receiving other anticancer treatment, the type of treatment and the dates of treatment will be reported on the CRF. The first follow-up visit will be in person and the rest of the follow-up visits may be done by telephone screening.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Changes to inclusion and exclusion criteria are indicated below and detailed in Section 17.

4.1. Patient Inclusion Criteria

Patients may be included in the study only if they meet all of the following criteria:

a. The patient has a confirmed diagnosis of Philadelphia chromosome (Ph) positive chronic myelogenous leukemia in either CP or AP. Accelerated phase will be defined as disease having 1 of the following: ≥15% to <30% blasts in peripheral blood or bone marrow; ≥30% blasts + promyelocytes in peripheral blood or bone marrow; ≥20% basophils in peripheral blood or bone marrow; platelet count <100x10^9/L unrelated to therapy; or clonal evolution.

b. The patient has either failed, demonstrated intolerance, or a combination of prior failure and intolerance, to prior treatments with at least 2 tyrosine kinase inhibitors (TKI's). Failure of TKI treatment may either be primary (never achieved a response) or secondary resistance (loss of response).

- TKI treatment failure will be defined as 1 of the following:
  - no CHR by 12 weeks (whether lost or never achieved)
  - no partial cytogenetic response by 24 weeks (ie, 1 to 35% Ph-positive) (whether lost or never achieved)
  - no major cytogenetic response by 52 weeks (ie, ≤35% Ph-positive) (whether lost or never achieved)
  - progressive leukocytosis, defined as increasing white blood cell (WBC) count on at least 2 consecutive evaluations, at least 2 weeks apart and doubling from the nadir to ≥20000/μL or absolute increase in WBC by ≥50000/μL above the post-treatment nadir
- Intolerance to TKI therapy will be defined as 1 of the following:
  - grade 3 to 4 nonhematologic toxicity that does not resolve with adequate intervention
  - grade 4 hematologic toxicity lasting more than 7 days, or a documented inability to sustain the TKI therapy because of recurrent grade 3 or 4 hematologic toxicity with re-initiation of the same therapy
  - any grade 2 or greater toxicity that is unacceptable to the patient
- Patients with a known T315I mutation must have been treated and failed ponatinib (prior to the entry into this study; this would not apply in a country where ponatinib has not been approved or where patients otherwise would not have access to this medication) unless medically contraindicated by the treating study doctor.

c. Patients must have completed all previous anticancer therapy for at least 2 weeks prior to the first planned dose of omacetaxine, except as noted below, and must have fully recovered from side effects of a previous therapy.

   - In patients with rapidly proliferating disease, hydroxyurea may be administered before study entry, if clinically indicated, to control disease. In such cases, CHR must be sustained for at least 4 weeks for accelerated CML, and at least 8 weeks for chronic phase CML, following the discontinuation of hydroxyurea, to be considered as a CHR.
   - Patients may receive anagrelide for up to 28 days (in countries where the product is registered). Leukapheresis is allowed up to 24 hours prior to the first treatment cycle with omacetaxine.

d. Patients must have adequate hepatic and renal function as evidenced by bilirubin 2.0 times the upper limit of the normal range (ULN) or lower, ALT and asparate aminotransferase (AST) 3 times the ULN or lower, serum creatinine 1.5 times the ULN or lower. Patients with nonclinically significant elevations of bilirubin up to 5.0 g/dL (85500 µmol/L) due to known or suspected Gilbert's disease are eligible; this must be documented on the medical history page of the CRF.

e. Patients must have an ECOG performance status of 0 to 2.

f. Patients are men or women at least 18 years of age.

g. Patients must be able and willing to provide written informed consent prior to any study related procedure. (In the event that the patient is re-screened for study participation or if a protocol amendment alters the care of an ongoing patient, a new informed consent form must be signed.)

h. Patients must be able to comply with the requirements of the entire study.

i. The patient must take precautions to not become pregnant or produce offspring. Women must be of non-childbearing potential (surgically sterile or postmenopausal for at least 12 months, confirmed by follicle-stimulating hormone [FSH] >40 IU/L) or agree to use a medically accepted method of contraception for the duration of the study and 90 days after treatment. Men must be surgically sterile or agree to use a medically accepted method of contraception for the duration of the study and 90 days after treatment. Acceptable methods of contraception include abstinence, barrier method with spermicide (excluding cervical cap and sponge), intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method.

4.2. Patient Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following criteria:

a. The patient has 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.

b. The patient has had a myocardial infarction in the previous 12 weeks. (Prior to study entry, any other electrocardiogram [ECG] abnormalities noted at screening other than myocardial infarction within the previous 12 weeks and felt by the investigator not to be medically relevant, must be documented as such.)

c. The patient has received radiotherapy within 30 days prior to the start of study drug, or has not recovered from the acute toxicities associated with prior approved therapies including investigational drugs.

d. The patient has another concurrent illness that would preclude study conduct and assessment, including, but not limited to, another active malignancy (excluding squamous or basal cell skin cancer and in situ cervical cancer), uncontrolled medical conditions, uncontrolled and active infection (considered opportunistic, life threatening, or clinically significant), uncontrolled risk of bleeding, or uncontrolled diabetes mellitus.

e. The patient underwent autologous or allogeneic stem cell transplant within 60 days prior to receiving the first dose of omacetaxine and has any evidence of ongoing graft versus host disease (GVHD), or GVHD requiring immunosuppressive therapy.

f. The patient has a human leukocyte antigen (HLA)-matched donor and is eligible for allogeneic transplantation for CML treatment.

g. The patient has known positive human immunodeficiency virus (HIV) or known active human t-cell lymphotropic virus (HTLV) I/II disease, whether on treatment or not.

h. The patient has known active hepatitis B or C. The determination of active hepatitis B or C is left to the investigator.

i. The patient is pregnant or lactating (any women becoming pregnant during the study will be withdrawn from the study).

j. The patient has any medical or psychiatric condition, which may compromise the ability to give written informed consent or to comply with the study protocol.

k. The patient has lymphoid Ph+ blast crisis or blast phase CML.

l. The patient participated in another clinical investigation within 30 days of enrollment or is receiving another investigational agent, unless discussed with the sponsor.

m. The patient received omacetaxine or has a history of hypersensitivity.

n. The patient has a known hypersensitivity to mannitol.

o. The patient has a hemoglobin value, which is, in the opinion of the investigator, not adequate given the pharmacokinetic blood draw requirements of the Phase 1 portion of the study.

p. The patient has undergone major surgery within 14 days prior to starting omacetaxine, or who has not recovered from side effects of such procedure.

4.3. Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the study at any time. The investigator also has the right to withdraw a patient from the study in the event of intercurrent illness, adverse events, pregnancy (see Section 7.3.4), or other reasons concerning the health or well-being of the patient, or in the case of lack of cooperation. In addition, a patient may be withdrawn from the study as described in Sections 3.6, 5.4, and 7.1.7.

Should a patient decide to withdraw after administration of study drug, or should the investigator decide to withdraw the patient, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given of why the patient is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from study drug treatment and the reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed onto the CRF. If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a clinically significant abnormal laboratory test result, monitoring will be continued at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The specific event or test result(s) must be recorded on the source documentation and transcribed onto the CRF.

5. TREATMENT OF PATIENTS

5.1. Study Drugs Administered

In Phase 1, there will be 3 cohorts of approximately 7 patients each. All patients will be given a fixed dose of 2.5 mg omacetaxine subcutaneous injection twice daily. The intent is to include, as much as possible, an equal number of patients in each BSA cohort. Cohort 1 will include patients whose BSA is less than 1.7 m^2. Cohort 2 will include patients with a BSA between 1.7 m^2 to 2.0 m^2 inclusive. Cohort 3 will include patients with BSA greater than 2.0 m^2.

Following the analysis of pharmacokinetic and preliminary safety and efficacy data from the Phase 1 patients reviewed by the independent DMC, a decision will be made whether to continue to the Phase 2 portion to further determine safety and efficacy. Refer to Sections 3.1 and 8, for further information on study design and pharmacokinetics, respectively.

For both phases (with the exception of cycle 1 of Phase 1 only), patients will receive induction cycles of 14 days twice daily treatment followed by 14 days without treatment (1 induction cycle) for as long as they adequately recover their blood counts and/or until they achieve hematologic response. Patients will then receive maintenance cycles of 7 days twice daily treatment followed by 21 days without treatment (1 maintenance cycle) for as long as they continue to benefit up to a period of 12 months following the first dose. Dose modifications for toxicity are allowed (see Section 5.1.2). If patients are continuing to receive benefit after 12 months, discussion with the sponsor must take place before continuing study agent administration or being given omacetaxine commercially available where omacetaxine is approved. Doses should be administered at 12 hour (±2 hour) intervals. Patients who miss 1 day of dosing can make up that missed day as long as there is no more than 1 day interruption in dosing. That dose can added at the end of that cycle as long as it is continuous.

For cycle 1 of Phase 1 only, patients will receive only 1 dose of omacetaxine on day 1, no doses on days 2 and 3, and 2 doses on days 4 through 17 due to the pharmacokinetic objectives of the study (see Table 3). Therefore, each patient will be scheduled to receive 29 doses during cycle 1.

In both phases, the first fixed dose (2.5 mg) of cycle 1 will be given as reconstituted by a healthcare professional (eg, investigational center pharmacist) in a syringe at the investigational center. All doses of study drug will be administered via a prefilled syringe with a fixed dose of omacetaxine. Some of these doses may be administered on an outpatient basis or away from the investigational center by the patient, health care provider, or caregiver (patient must have been carefully trained before subcutaneous administration [see Section 5.1.1]) with a prefilled syringe reconstituted by applicable trained study healthcare professionals. The patient will record omacetaxine injections on a diary, which will be supplied for this purpose. The patient will return to the investigational center to obtain prefilled syringes (as per the expiration date).

Omacetaxine must be reconstituted by a healthcare professional. Proper aseptic technique should be used. Avoid contact with the skin. If omacetaxine comes into contact with skin, immediately and thoroughly wash affected area with soap and water.

Omacetaxine does not contain antimicrobial preservatives. Therefore, care must be taken to ensure that the solution for injection is not contaminated during preparation.

Omacetaxine is an antineoplastic product. Caution should be used during handling and preparation.

Information regarding reconstitution, handling, shipping, and disposal of the syringe will be provided to the investigational center personnel.

5.1.1. Training for the Patient or Caregiver

Omacetaxine will be administered by subcutaneous injection twice daily. The first dose of cycle 1 will be administered at the investigational center. Subsequent doses (in prefilled syringes) may be administered away from the investigational center after training takes place. For day 1 of each cycle patients come to the investigational center to obtain drug and perform the required tests as applicable. If patients have difficulty after they undergo training, and in absence of a caregiver, they may be asked to come to the investigational center more often until they demonstrate proper technique.

The dose will be prepared in a commercially available 1-mL syringe by a healthcare professional and the fixed dose will be constant across all patients. The expiration date and time should be checked by the healthcare professional, caregiver, or patient before administration. The syringe may be carried in a tray within a container that will maintain the recommended storage conditions for omacetaxine. The patient will return to the investigational center to obtain prefilled syringes (as per the expiration date). Further details of this information will be available in a Pharmacy Manual or pharmacy section of the investigator's file at the investigational center including the most current stability data of the reconstituted omacetaxine.

Omacetaxine is to be administered by subcutaneous injection. The injection site should be disinfected with an alcohol swab, and allowed to air dry before the injection. The healthcare provider, caregiver, or the patient will be instructed to choose 1 of the following anatomical sites for the injection: thighs, abdomen, or back of the upper arms. The healthcare provider, caregiver, or the patient should select a new site before each injection. Any new injection must be done at least 3 cm from a previous injection site. The healthcare provider, caregiver, or the patient will be instructed not to inject study drug in areas where the skin have bruises, is sensitive, red, or indurated.

The patient and/or caregiver will be carefully trained before the subcutaneous administration. Retraining as a refresher for investigational centers or patients will take place frequently and at least once per year for investigational centers that have active patients, but also as needed if issues arise via monitoring of the diaries, or monitoring of the investigational pharmacies. A training pamphlet with illustrations of the administration of a subcutaneous injection will be made available to the investigational centers and the patients or caregivers. Instructions on how to fill out the diary for accurate recording of doses administered will also be made available to investigational centers and patients.

The patient will record omacetaxine injections in a diary, which will be supplied for this purpose. The diaries will be requested and reviewed by investigational centers at approximately weekly visits or more frequently if a patient has difficulties in the beginning. Further training will also be available. Applicable information from the diary will be entered into the clinical database. To ensure compliance of the reconstituted doses of omacetaxine and required procedures, outpatient nursing services, when needed, may be provided by the sponsor or reimbursed by the sponsor, depending on where the patient lives.

5.1.2. Dose Modifications for Toxicity

5.1.2.1. Hematologic Toxicity

Omacetaxine treatment cycles may be delayed and/or the number of days of dosing during the cycle reduced for hematologic toxicities (eg, neutropenia, thrombocytopenia).

Complete blood counts should be performed weekly during the first 5 cycles. After the initial 5 cycles, CBCs should be performed every 2 weeks (±2 days) or as clinically indicated via unscheduled but collected data visits. If a patient experiences grade 4 neutropenia (absolute neutrophil count [ANC] less than $0.5x10^9$/L) or grade 3 thrombocytopenia (platelet counts less than $50x10^9$/L) during a cycle, delay starting the next cycle until ANC is greater than or equal to $1.0x10^9$/L and platelet count is greater than or equal to $50x10^9$/L. If the patient should experience a delay as just described, in the next cycle, the number of dosing days can be reduced by 2 days. For example, during induction this would be from 14 days to 12 days; during maintenance, this would be from 7 days to 5 days. If subjects tolerate a cycle with a 2-day reduction without any problems, then the following cycle, the full cycle can be provided. If more than 2 delays occur secondary to grade 4 neutropenia or grade 3 thrombocytopenia with yet another reduction in 2 more days in either induction or maintenance, consideration of discontinuing study medication should be discussed by the treating physician, the designated CRO physician, and the designated Sponsor physician.

5.1.2.2. Nonhematologic Toxicity

Other clinically significant nonhematologic toxicity will be managed on the basis of symptoms. Interrupt and/or delay omacetaxine until toxicity is resolved.

Complete blood count monitoring may be changed to every second week as clinically indicated during treatment starting with cycle 6.

5.2. Restrictions

There are no specific restrictions in this study other than those described above and below.

5.3. Prior and Concomitant Therapy or Medication

Any prior or concomitant therapy, medication, or procedure a patient has had within 14 days before study drug administration or during study drug administration, will be recorded on the CRF. During follow-up, any new anticancer treatments will be recorded. Generic or trade name,

indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHO Drug).

Avoid anticoagulants, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) when the platelet count is less than 50000/μL as they may increase the risk of bleeding.

Omacetaxine can induce glucose intolerance. Patients already being treating for diabetes, or patients with risk factors for diabetes, must have their blood glucose levels checked frequently.

5.3.1. Permitted Concomitant Medications

The following concomitant medications are allowed during the study:

- For patients with rapidly proliferating disease, hydroxyurea may be administered immediately prior to and during the first 2 cycles of treatment, if clinically indicated, to control disease. In such cases, CHR must be sustained for at least 4 weeks for accelerated phase CML and for at least 8 weeks for chronic phase CML, following the discontinuation of hydroxyurea, to be considered as a CHR.

- Patients may receive anagrelide for up to 28 days (in countries where the product is registered).

- Leukapheresis is allowed up to 24 hours prior to the first treatment cycle with omacetaxine.

- All medications necessary for the treatment of other chronic patient conditions should be administered at a stable dose for 30 days prior to the first study drug administration and during the course of study treatment. Any major changes need to be discussed with the medical monitor.

- Premedication with antiemetic therapy will be permitted if clinically indicated. All such medications should be noted and recorded on the appropriate case report form.

- Hematopoietic growth factors may be used for treatment of febrile neutropenia; they may not be used to prophylactically maintain the white blood cell count.

- Erythropoietin or darbepoetin alfa may be used and /blood transfusions administered at any time for treatment of anemia except 24 hours before a pharmacokinetic blood sample is drawn.

These requirements do not exclude the use of appropriate medications for the treatment of adverse events and/or intercurrent illness under the direction of the principal investigator.

5.3.2. Prohibited Medications

Systemic chemotherapy in the 2 weeks prior to the first study drug administration of omacetaxine and during the course of study treatment is prohibited.

5.4. Procedures for Monitoring Patient Compliance

Each investigator will be responsible for monitoring patient compliance and assisting the sponsor with accurate record keeping of administration of omacetaxine. A check of study drug compliance will be performed during each visit after the initial dispensation of study drug, and study drug accountability records will be completed. If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn. Patients will also be notified of these requirements in the informed consent process. The IEC/IRB should be notified.

5.5. Total Blood Volume

The total blood volume to be withdrawn for any given patient is difficult to accurately predict and will depend, among other things, on how long the patient receives study drug, whether there are any adverse events leading to unscheduled blood draws, and whether there is any hospitalization related to said adverse events. Therefore, the timing and quantity obtained are defined in general terms as follows:

Full serum chemistry laboratory tests are scheduled to be performed at screening, every 2 weeks (±2 days) after cycle 5, and at the end-of-treatment visit. At each time point, 6 to 7 mL of blood will be drawn.

Serum chemistry 7 laboratory tests are scheduled to be performed on day 1 of each cycle, and days 7 (±2 days), 14 (±2 days), and 21 (±2 days) of cycles 1 through 5. At each time point, 6 to 7 mL of blood will be drawn.

Hematology laboratory tests are scheduled to be performed at screening, day 1 of each cycle, days 7 (±2 days), 14 (±2 days), and 21 (±2 days) of cycles 1 through 5, day 14 (±2 days) for cycles after cycle 5, at confirmation of response, and at the end-of-treatment visit. At each time point, 4 to 5 mL of blood will be drawn.

BCR-ABL transcript levels are scheduled to be performed at screening, every 3 months (ie, every 3 cycles) during the study, at confirmation of response, and at the end-of-treatment visit. At each time point, 3 mL of blood will be drawn.

BCR-ABL mutation analysis is to be performed at screening and every 3 months (ie, every 3 cycles) on study. At each time point 3mL of blood will be drawn.

A serum pregnancy test for all women of childbearing potential may be performed at screening (a urine pregnancy test is also acceptable); 2 mL of blood will be drawn.

Pharmacokinetic blood samples are scheduled to be performed at 15 time points during cycle 1 of Phase 1, at 4 time points per cycle during cycles 2 and 3 of Phase 1, and at 4 time points per cycle during cycles 1, 2, and 3 of Phase 2. At each time point, 2.5 mL of blood will be drawn.

As an example and assuming an average number of cycles of 4 per patient, the total blood volume for a patient in Phase 1 receiving 4 cycles of treatment would be 233.5 mL to 269.9 mL. The total blood volume for a patient in Phase 2 receiving 4 cycles would be 216 mL to 252 mL.

6. ASSESSMENT OF EFFICACY

6.1. Primary Efficacy Variables

The primary efficacy variables and endpoints for this study are as follows:

- For patients with CP CML, the proportion of patients who achieve a major cytogenetic response (MCyR: complete cytogenetic response with no Ph+ metastases and partial cytogenetic response with up to 35% Ph+ metaphases) at any time during the study.
- For patients with AP CML, the proportion of patients who achieve a major hematologic response (MaHR: complete hematologic response or no evidence of leukemia) and/or MCyR at any time during the study.
- Final determination of response will be made by the independent DMC, comprised of 3 physicians who treat patients with CML, are experienced with this type of activity, and are not investigators in the study. The method for response review will be detailed in the DMC Charter.

Response evaluation criteria are described in Appendix A.

6.2. Secondary Efficacy Variables

The secondary efficacy variables and endpoints for this study are as follows:

- duration of response
- progression-free survival
- overall survival
- molecular response at any time during the study

6.2.1. Duration of Response

Duration of response is defined for responders as the time interval from the first reported date of MCyR or MaHR, as defined above, to the earliest date of objective evidence of disease progression (ie, development of accelerated-phase CML), relapse (ie, loss of complete hematologic or major cytogenetic response), or death. Patients who have an ongoing response or patients who discontinue treatment for reasons other than adverse events, progression, or death will have their data censored at the last response assessment date.

6.2.2. Progression-Free Survival

Progression-free survival is defined as the time interval from the date of first dose to the date of the earliest objective evidence of disease progression (ie, development of accelerated-phase CML), relapse (ie, loss of complete hematologic or major cytogenetic response), or death. Patients who do not have disease progression or patients who discontinue treatment for reason other than adverse events, progression, or death will have their data censored at the last response assessment date.

6.2.3. Overall Survival

Overall survival is defined as the time interval from the date of the first dose to the date of death from any cause. Patients who do not die at the time of analysis will have their data censored at the last known alive date.

6.2.4. Molecular Response

Molecular response is defined by the decrease in the amount of BCR-ABL mRNA measured by reverse transcriptase polymerase chain reaction (RT-PCR) or by the actual percentage of BCR-ABL mRNA transcripts (ratio of BCR-ABL transcript numbers to the number of control gene transcripts) (Baccarani et al 2013, Cross et al 2012, Hughes et al 2006) (see Appendix A).

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study staff by evaluating the following:

- adverse events (type, frequency, severity, and causality)
- clinical laboratory test results (serum chemistry and hematology) at various points in the study
- vital signs measurements (blood pressure, heart rate, respiratory rate, body temperature)
- body weight
- physical examination (including body weight)
- 12-lead ECG
- concomitant medication usage
- ECOG performance status

During the conduct of the study, an independent DMC will review accumulating safety and efficacy data on a regular basis (depending on percent of patients enrolled, or as described in the DMC charter) to ensure the safety of the study patients and study conduct issues. The DMC will also review data (pharmacokinetic, preliminary safety and efficacy) in Phase 1 in order to decide if the study is to continue to Phase 2 portion or be terminated.

The DMC will be composed of independent physicians with expertise in the CML therapeutic field. The DMC will receive safety and efficacy data, and other ad hoc data requested, as described in the charter. They will have the right to recommend discontinuation of the study for safety reasons.

The DMC chairperson will communicate with the sponsor in regard to issues resulting from the conduct and clinical aspects of the study. The sponsor will work closely with the committee to provide the necessary data for review.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

In this study, any adverse event occurring after the clinical study patient has signed the informed consent form should be recorded and reported as an adverse event.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during the study will not be considered adverse events.

Accordingly, an adverse event could include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions. (Note: A condition, recorded as pre-existing, that is intermittently symptomatic [eg, headache] and which occurs during the study should be recorded as an adverse event.)
- drug interactions
- events occurring during diagnostic procedures or any washout phase of the study
- laboratory or diagnostic test abnormalities occurring after the start of the study (ie, after screening and once confirmed by repeat testing) that results in the withdrawal of the patient from the study, requires medical treatment or further diagnostic work-up, or is considered by the study Investigator to be clinically significant. Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events, but will be recorded to monitor data from patients who do not meet screening criteria.
- all events of possible drug induced liver injury with hyperbilirubinemia (defined as AST or ALT ≥3 times ULN, plus either bilirubin ≥2 times the ULN or International Normalized Ratio [INR] >1.5) or Hy's Law events require immediate study treatment cessation and reporting as a serious adverse event.

Disease progression (or progressive disease), including death from disease progression, will not be considered an adverse event or a serious adverse event in this study, but will be collected as an efficacy variable, unless the outcome is more serious than what would normally be expected from the normal course of the disease.

7.1.2. Recording and Reporting Adverse Events

For the purpose of adverse event recording, the study period is defined as that time period from signature of the informed consent form through the end-of-treatment visit. Additional follow-up is without treatment for 12 months after the last treatment cycle or until death.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF, regardless of the severity of the event or judged relationship to the study drug. For serious adverse events, the Serious Adverse Event Form must also be completed and the serious adverse event must be reported immediately (see Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

At each contact with the patient, the investigator or designee must query the patient for adverse events by asking an open ended question such as, “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the Serious Adverse Event Form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to baseline, or until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed onto the CRF.

The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the Investigator, must be recorded as described below.

7.1.3. Severity of an Adverse Event

The severity of each adverse event will be graded according to the NCI CTCAE version 4.0.

Adverse events that are not included in the NCI CTCAE lists will be graded according to the NCI CTCAE general guideline for grades as follows:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local intervention, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL, eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to adverse event.

7.1.4. Relationship of an Adverse Event to the Study Drug

The relationship of an adverse event to the study drug is characterized as follows:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the study drug. • It could readily have been produced by the patient's clinical state, environmental, or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the study drug. • It does not reappear or worsen when the drug is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the study drug administration cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the study drug. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental, or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet a drug relationship clearly exists. • It follows a known pattern of response to the study drug.

7.1.5. Serious Adverse Events

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (ie, the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered serious adverse events.
- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered serious adverse events.

A visit to the hospital emergency room or hospital clinic is not considered inpatient hospitalization; however, it could be considered a serious adverse event if medical intervention was necessary in order to prevent a serious outcome, or if the patient was hospitalized. Thus, observation is not considered a serious adverse event.

7.1.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The reference safety information for this study is the current Investigator's Brochure.

The sponsor's Global Patient Safety & Pharmacovigilance Department will determine the expectedness for all serious adverse events.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events (as described in Section 7.1.5.1) that occur during the study period (including the protocol-defined follow-up period, described in Section 7.1.2), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or other designated personnel (a contract research organization [CRO] in a country without a Sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's Global Patient Safety & Pharmacovigilance Department..

The following information should be provided to record the event accurately and completely:

- study number C41443/2057
- investigator and investigational center identification
- patient number
- patient initials
- onset date and description of adverse event
- investigator's assessment of the relationship of the adverse event to the study drug (no reasonable possibility, reasonable possibility)

Additional information may include the following:

- age and sex of patient

- date of first dose of study drug
- date and amount of last administered dose of study drug
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant therapy (including doses, routes, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death:
  - cause of death (whether or not the death was related to study drug)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigational center within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's Global Patient Safety & Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/ extensible markup language (XML) file to the LSO/CRO for local submission to the regulatory authorities and IEC/IRBs and Investigators, according to regulations. The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with local regulations.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.2).

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all Investigators participating in sponsored clinical studies of omacetaxine and the appropriate regulatory authorities (and IEC/IRB, if appropriate).

In addition to notifying the investigators and regulatory authorities (and IEC/IRB, if appropriate), other measures may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- altering the process of informed consent by modifying the existing consent form and informing current study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to omacetaxine

7.1.6. Protocol-Defined Adverse Events for Expedited Reporting

No protocol defined adverse events for expedited reporting were identified for this study.

7.1.7. Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from omacetaxine and/or the study at any time at the discretion of the investigator. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse event page and termination page (end-of-treatment termination and/or study termination) of the CRF will be completed at that time, especially if the patient may not be able to come back for the regularly scheduled end-of-treatment visit.

The patient will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The investigator must inform the clinical project physician (CPP)/clinical leader (CL) as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from omacetaxine for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event which in the opinion of the investigator is not severe enough to warrant discontinuation but which requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be need to take a prohibited medication, not the adverse event.

7.1.8. Medical Emergencies

Medical emergencies must be reported to the individual identified in the clinical study personnel contact information section of this protocol.

Equipment, supplies, and properly skilled medical personnel must be accessible for an adverse event requiring immediate treatment. Any dose of study drug, whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.

7.1.9. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, departures from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment has been administered to ensure patient safety, the investigator or other physician in attendance must contact the individual identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.2. Pregnancy

All pregnancies (pregnancies of women participating in the study and partners of men participating in the study) that occur during the study, or within 90 days of completion of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the LSO/CRO with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event (see Section 7.1.5.3).

Any patient becoming pregnant during the study will be withdrawn. All patients (or partners) who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), details of birth, and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form.

7.3. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range allowed for this study for this patient population will be interpreted by the investigator as belonging to 1 of the following categories:

- abnormal but not a clinically significant worsening from baseline
- abnormal and a clinically significant worsening from baseline

A laboratory test result that has significantly worsened (according to medical judgment) from the baseline result will be recorded on the source documentation, transcribed onto the CRF as an adverse event, and monitored as described in Section 7.1.2. An adverse event includes a laboratory or diagnostic test abnormality (once confirmed by repeat testing) that results in the withdrawal of the patient from the study, the temporary or permanent cessation of treatment with study drug, or medical treatment or further diagnostic work-up.

Clinical laboratory tests (serum chemistry and hematology) will be performed at screening, prior to each treatment cycle, every 7 days (±2 days) during the first 5 cycles, and every 2 weeks (±2 days) during later cycles, as clinically indicated, and at the end-of-treatment visit. Urinalysis will be performed at screening only.

Additional serum chemistry and hematology tests will be performed as clinically indicated in the case of severe toxicity until toxicity (or follow-up for an adverse event) resolves, returns to the baseline value, or grade 1 toxicity. These will be recorded on unscheduled CRF pages.

Additional hematology laboratory tests may be performed (and collected) to follow cytopenia at the discretion of the investigator or follow-up of an adverse event such as infection. These will be recorded on unscheduled CRF pages.

Clinical laboratory tests will be performed using local laboratories. Specific laboratory tests to be performed are listed below.

7.3.1. Serum Chemistry

The following serum chemistry tests will be performed, unless otherwise specified:

- phosphorus
- sodium
- potassium
- chloride
- bicarbonate or carbon dioxide
- glucose

- blood urea nitrogen (BUN) or urea
- creatinine
- uric acid
- ALT
- AST
- total bilirubin
- direct bilirubin, if clinically indicated
- indirect bilirubin, if clinically indicated

7.3.2. Hematology

The following hematology tests will be performed:

- hemoglobin
- hematocrit
- red blood cell (RBC) count
- platelet count
- ANC
- white blood cell (WBC) count and differential count
  - polymorphonuclear leukocytes (neutrophils)
  - lymphocytes
  - eosinophils
  - monocytes
  - basophils
  - Other (see Appendix D)

7.3.3. Urinalysis

Urinalysis, performed only at screening, will include testing for the following:

- protein
- glucose
- ketones
- blood (hemoglobin)
- pH
- specific gravity
- microscopic, only if clinically indicated
  - bacteria
  - RBCs
  - WBCs
  - casts
  - crystals

7.3.4. Other Clinical Laboratory Tests

Other clinical laboratory tests will be performed to ensure the safety of the patients, but will not be used to assess the safety of the study drug.

Human chorionic gonadotropin (HCG) urine tests or beta HCG (βHCG) serum tests will be performed for all women at screening and thereafter, if clinically indicated. Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

7.4. Vital Signs

Vital signs include the following:

- heart rate
- respiratory rate
- seated blood pressure
- body temperature

Before pulse and blood pressure are measured, the patient must be in a supine or semi-erect/seated position and resting for at least 5 minutes. (The same position and arm should

be used each time vital signs are measured for a given patient.) For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as a clinically significant change (worsening) from a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

7.5. Electrocardiography

A 12 lead ECG will be conducted at screening, prior to dosing on day 1 of cycles 1 through 3, optionally after completion of treatment on day 14 of cycle 1, every 3 months (ie, every 3 cycles) during the study, and at the end-of-treatment visit. Prior to study entry, any other ECG abnormalities noted at screening other than myocardial infarction within the previous 12 weeks and felt by the investigator not to be medically relevant, must be documented as such. In countries where required, ECGs will be performed before and after every cycle (±3 days) or more frequently as clinically indicated. Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.6. Physical Examinations

Physical examinations, including body weight (and height to be obtained at the screening visit only) will be performed as in the schedule of events Table 2. Physical examination findings at screening will be classified using standard categories as listed on the Medical History CRFs. Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, recorded on the Adverse Event CRF, and monitored as described in Section 7.1.2.

7.7. Concomitant Therapy or Medication

Concomitant therapy or medication usage will be monitored throughout the study. Details of prohibited medications are found in Section 5.3.

7.8. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be assessed at screening, day 1 of each cycle, and at the end-of-treatment visit.

7.9. Methods and Timing of Assessing, Recording, and Analyzing Safety Data

Methods and timing of assessing safety data are discussed in Section 3.11. Procedures for recording safety data are discussed in Section 13.1, and methods of analyses are discussed in Section 9.8.

Furthermore, all adverse events will be reviewed on a periodic basis (eg, scheduled safety reviews for omacetaxine) as interim/preliminary safety databases become available (see Section 7).

8. ASSESSMENT OF PHARMACOKINETICS

To characterize the pharmacokinetics of omacetaxine, blood samples (2.5 mL) for measurement of plasma concentrations of omacetaxine and its 2 known circulating metabolites, 4'-DMHHT and cephalotaxine, will be obtained (via venipuncture or indwelling catheter) as specified below in Section 8.2. The actual time, dose, and volume of omacetaxine administered and actual blood collection time will be documented on CRFs.

8.1. Pharmacokinetic Variables

The following pharmacokinetic parameters for omacetaxine and its metabolites will be calculated for each patient, when possible, from plasma concentrations obtained following the first dose of omacetaxine in Phase 1:

- maximum observed plasma drug concentration (C_{max}) by inspection (without interpolation)
- time to C_{max}, by inspection (t_{max})
- area under the plasma drug concentration by time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$)
- AUC from time 0 to the time of the last measurable drug concentration (AUC_{0-t})
- AUC from time 0 to 12 hours (AUC_{0-12})
- apparent plasma terminal elimination rate constant (λ_z) and associated terminal elimination half-life ($t_{½}$)
- percentage extrapolation calculated as $(AUC_{0-\infty}-AUC_{0-t})/(AUC_{0-\infty})x100$
- apparent plasma clearance (CL/F)
- apparent volume of distribution (V_z/F)
- predicted accumulation ratio (R_{pred}) calculated as $AUC_{0-\infty}/AUC_{0-12}$

8.2. Blood Sampling and Handling

Methods for blood sampling and processing are in the Pharmacokinetics and Laboratory Manual.

8.2.1. Phase 1

In Phase 1, to accommodate the pharmacokinetic objective of the study, during cycle 1, omacetaxine will be administered by subcutaneous injection as follows: 1 dose will be administered in the morning of day 1, no doses will be administered on days 2 or 3, 2 doses will

be administered on days 4 through 17. Starting with cycle 2, patients will continue treatment as in Section 5.1.

Blood samples (2.5 mL) will be obtained during Phase 1 as follows (see Table 3):

- 20 minutes prior to and 15 (±5 min), 30 (±5 min), and 45 (±5 min) minutes and 1 (±5 min), 2 (±10 min), 4 (±10 min), 8 to 12 (±15 min), 24 (±1 hr), 48 (±1 hr), and 72 (±1 hr) hours (predose 1 on day 4) after administration of the first dose of omacetaxine
- on day 10 or 11 or 12, predose, within (<) 1 hour after dose 1, and 1 to 12 hours after dose 1
- 1 sample on day 13, 14, 15, 16, or 17 either predose 1 or predose 2

In addition, blood samples (2.5 mL) will be obtained in Phase 1 on day 1 of cycles 2 and 3 as follows (see Table 4):

- within (<) 1 hour after dose 1
- 1 to 12 hours after dose 1
- 1 sample either predose 1 or predose 2 on any day after day 1 during week 1
- 1 sample either predose 1 or predose 2 on any day during week 2

8.2.2. Phase 2

Blood samples (2.5 mL) will be obtained in Phase 2 on day 1 of cycles 1, 2, and 3 as follows (see Table 4):

- within (<) 1 hour after dose 1
- 1 to 12 hours after dose 1
- 1 sample either predose 1 or predose 2 on any day after day 1 during week 1
- 1 sample either predose 1 or predose 2 on any day during week 2

8.3. Shipment of Samples

Procedures for shipment and processing of samples are in the Pharmacokinetics and Laboratory Manual.

9. STATISTICS

9.1. Study Design

This is a Phase 1/Phase 2 open-label, single-group clinical study in patients with CP or AP CML who have failed 2 or more TKI therapies to investigate the pharmacokinetics, safety, and efficacy of omacetaxine given subcutaneously as fixed doses.

9.2. Sample Size and Power Considerations

The sample size for Phase 1 is approximately 21 patients in order to meet the pharmacokinetic objectives of the study. These 21 patients will also be counted in the sample size for Phase 2 and be part of any Phase 2 analyses.

Phase 2 sample sizes are based on Simon's 2-stage optimum design. To reject the null hypothesis of MCyR rate 2.5% or lower in patients with CP CML at a target 1-sided alpha of 0.025 and beta of 0.10 (power of 90%) and assuming that the MCyR rate in the current study will be at least 16%, in the first stage 16 patients with CP CML will be treated. If 1 or more patients respond, then the study will enroll another 29 patients with CP CML for a total of 45 patients. If 4 or more of the 45 patients achieve a MCyR, the fixed-dose regimen will be deemed effective in patients with CP CML. If the true rate is less than or equal to 2.5%, the probability of stopping after stage 1 is 0.667.

The alternative hypothesis rate is set at 16% because an 18.4% response rate was observed in the registration studies (Studies CGX-635-CML-202 and CGX-635-CML-203) in which patients received older generations of TKI drugs, and in the current study patients will be more likely to have received a newer generation of TKI drugs and more lines of therapy and may be less likely to respond to omacetaxine.

To reject the null hypothesis of MCyR rate 2.5% or lower in patients with AP CML at a target 1-sided alpha of 0.025 and beta of 0.10 (power of 90%), and assuming that the MaHR rate in the current study will be at least 12%, in the first stage 40 patients with AP CML will be treated. If 2 or more patients achieve a MaHR, then the study will enroll another 27 patients with AP CML for a total of 67 patients. If 5 or more of the 67 patients respond, then the drug will be deemed to be effective in patients with AP CML. If the true rate is 2.5% or lower, the probability of stopping after stage 1 is 0.736. The alternative hypothesis rate is set at 12%, lower than the observed rate of 14.3 in the above mentioned registration studies for the same reason.

9.3. Analysis Sets

The set of enrolled patients includes all patients who provide informed consent to participate in the study and who meet all inclusion and exclusion criteria, regardless of whether or not a patient receives any study drug.

The safety analysis set will include patients who receive 1 or more doses of study drug.

The per-protocol analysis set will include patients in the safety analysis set who have at least 1 response assessment after study drug administration and have been compliant with the study protocol.

The pharmacokinetic analysis set will include all patients who have at least 1 pharmacokinetic measurement value after receiving study drug.

9.4. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data. Patients without response assessment after dosing will be considered nonresponders.

9.5. Study Population

The set of enrolled patients (see Section 9.3) will be used for all study population summaries unless otherwise noted. Summaries will be presented by BSA categories and overall in Phase 1, by disease phase (CP CML and AP CML), and overall in Phase 2, as appropriate.

9.5.1. Patient Disposition

Data from patients who are enrolled, patients enrolled but not treated, patients in the safety, per-protocol, and pharmacokinetic analysis sets, patients who complete the study, and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

9.5.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications, and ECG findings will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

9.6. Efficacy Analysis

Efficacy variables will be calculated using the safety analysis set and the per-protocol analysis set and be displayed by disease phase.

9.6.1. Primary Variables

The primary efficacy variable for patients with CP CML is the proportion of patients who achieve a major cytogenetic response (MCyR: complete cytogenetic response with no Ph+ metastases and partial cytogenetic response with up to 35% Ph+ metaphases). The primary efficacy variable for patients with AP CML is the proportion of patients who achieve a major

hematologic response (MaHR: complete hematologic response or no evidence of leukemia) and/or MCyR.

9.6.2. Secondary Variables

The secondary efficacy variables are as follows:

- duration of response, defined for responders as the time interval from the first reported date of MCyR or MaHR, as defined above, to the earliest date of objective evidence of disease progression (ie, development of accelerated-phase CML), relapse (ie, loss of complete hematologic or major cytogenetic response), or death
  Patients who have ongoing response or patients who discontinue treatment for reasons other than adverse events, progression, or death will have their data censored at the last response assessment date.

- progression-free survival, defined as the time interval from the date of the first dose to the earliest date of objective evidence of disease progression (ie, development of accelerated-phase CML), relapse (ie, loss of complete hematologic or major cytogenetic response), or death
  Patients who do not have disease progression or patients who discontinue treatment for reason other than adverse events, progression, or death will have their data censored at the last response assessment date.

- overall survival, defined as the time interval from the date of first dose to the date of death from any cause
  Patients who do not die at the time of analysis will have their data censored at the last known alive date.

- molecular response, defined by the decrease in the amount of BCR-ABL mRNA measured by RT-PCR (reverse transcriptase polymerase chain reaction) or by the actual percentage of BCR-ABL mRNA transcripts (ratio of BCR-ABL transcript numbers to the number of control gene transcripts) (Baccarani et al 2013; Cross et al 2012, Hughes et al 2006) (see Appendix A)**.**

9.6.3. Planned Method of Analysis

Response rates by disease phase (CP CML and AP CML) and their 2-sided exact 95% CIs will be calculated. The lower limit of the CI will be compared with a prior value of 2.5%. If the lower limit exceeds 2.5%, the observed response rate will have exceeded the minimum threshold required to demonstrate efficacy. When sample size permits, these variables will also be compared within a disease phase by age, sex, disease history, and treatment history using a logistic regression model.

For duration of response, time to progression, and overall survival, the Kaplan-Meier method will be used to calculate survival rates by disease phase. When sample size permits, these variables will also be compared within a disease phase by age, sex, disease history, and treatment history using a Cox proportional hazards regression model.

Molecular responses will be analyzed using descriptive statistics.

Efficacy variables will also be analyzed separately in patients who were treated in Phase 1.

Additional exploratory analyses may be performed to assist in planning future studies.

9.7. Multiple Comparisons and Multiplicity

There are no multiple comparisons or multiplicity in this study.

9.8. Safety Variables and Analysis

The safety and tolerability of omacetaxine treatment will be assessed throughout the study by evaluating the following:

- adverse events (type, frequency, severity, and causality)
- clinical laboratory test results (serum chemistry and hematology) at various points in the study
- vital signs measurements (blood pressure, heart rate, respiratory rate, body temperature)
- bodyweight
- 12-lead ECG
- concomitant medication usage
- ECOG performance status

The safety analysis set will be used for all safety analyses. Safety data will be displayed by disease phase and overall.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to study drug treatment (ie, related, not related, or with missing relationship) (overall and by severity), serious adverse events, serious treatment-related adverse events, adverse events leading to withdrawal, and grade 3 and 4 adverse events. Patient listings of adverse events, serious adverse events, and adverse events leading to withdrawal will be presented.

Laboratory values will be graded according to NCI CTCAE version 4.0 criteria. The number and percentage of patients with grade 3 or 4 values will be tabulated. Summaries of laboratory values for laboratory parameters will be provided. Vital signs abnormalities will be categorized and tabulated. Summaries of the vital sign measurements will be provided. Changes in ECOG

performance status will be identified as improved, worsened, or stayed the same, and incidences of patients with changes will be tabulated.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with study drug.

For continuous variables, descriptive statistics (n, mean, standard deviation, standard error, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

If any patient dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the patient narrative included in the clinical study report.

Safety variables will also be analyzed separately in patients who were treated in Phase 1.

9.9. Pharmacokinetic Analysis

The pharmacokinetic analysis set will be used for all pharmacokinetic analyses. Pharmacokinetic parameters will be summarized by BSA categories and overall using descriptive statistics. All plasma concentration data may also be included in population pharmacokinetic analyses to further characterize the pharmacokinetics of omacetaxine in the patient populations and to assess exposure-response and exposure-safety relationship in patients receiving omacetaxine, if appropriate.

9.10. Planned Interim Analysis

Pharmacokinetic and pharmacodynamic analyses as appropriate will be conducted to monitor patients during Phase 1 of the study. As each patient completes cycle 1 in Phase 1, plasma concentrations of omacetaxine will be measured. A few patients may be batched. The difference between expected and measured pharmacokinetic data will be used to determine if the fixed dose strategy is appropriate, or whether alternative strategies are warranted. If differences emerge, analyses will be conducted to determine if the deviations can be explained by differences in BSA.

Once a total of approximately 21 patients with adequate pharmacokinetic samples are enrolled in Phase 1 of the study, pharmacokinetic parameters will be determined. Some patients may be replaced. Whether or not there is any correlation between exposure and preliminary efficacy or safety will be explored.

After all patients in Phase 1 have completed cycle 1 of treatment and have pharmacokinetic samples analyzed, descriptive statistics will be used to compare pharmacokinetic parameters among the 3 cohorts (patients with small, medium, and large BSA). No formal statistical testing will be done due to the small sample size. Selected preliminary safety and efficacy data, as

appropriate, will also be provided to the DMC to assist with the evaluation of whether the fixed dose is appropriate for Phase 2 of the study.

9.11. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the complete statistical plan, the clinical study report, or any combination of these, as appropriate.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The medical experts, study monitors, auditors, and health authority inspectors (or their agents) will be given direct access to source data and documentation (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

Each investigator must maintain the original records (ie, source documents) of each patient's data at all times. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, diary data, protocol required worksheets, and CRFs that are used as the source (see Section 3.9).

Each investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept until notification by the sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol Amendments and Protocol Deviations and Violations

11.1.1. Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB, except when necessary to address immediate safety concerns to the patients or when the change involves only logistics or administration. The investigator and the sponsor will sign the protocol amendment.

11.1.2. Protocol Deviations

Any significant deviation from the protocol will be considered a protocol violation. Protocol violations include nonadherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to study drug administration; use of prohibited medications; or any other deviations that may have an impact on the processes put in place for the care and safety of the patients. Protocol violations will be identified and recorded by investigational center personnel on the CRF. All protocol violations will be reported to the responsible IEC/IRB, as required.

When a protocol violation is reported, the sponsor will determine whether to discontinue the patient from the study or permit the patient to continue in the study, with documented approval from the medical representative. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Deviations from the inclusion/exclusion criteria of the protocol are not prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol eligibility criteria was entered into a study, they must immediately inform the sponsor of the protocol violation. If such patient has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded.

11.2. Information to Study Personnel

Each investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new staff become involved). Each investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the investigational center authorization form, which includes a clear description of each staff member’s responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including each investigator, and for ensuring they comply with the protocol. Additional information will be

made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

11.3. Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the informed consent form and the study is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and each investigator. The main responsibilities of the study monitors are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitors will contact the investigator and visit the investigational center at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (CRFs and other pertinent source data records, to include specific electronic source documentation [see Section 3.9]) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. If electronic CRFs are used for the study, the study monitor will indicate verification by electronically applying source document verification (SDV) flags to the CRF and will ensure that all required electronic signatures are being implemented accordingly.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. Each investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits and/or provided in follow-up written communication.

11.4. Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCPs, and applicable regulatory requirements. The sponsor Global Clinical Quality Assurance department, independent of the Global Clinical Development department, is responsible for determining the need for (and timing of) an investigational center audit.

Each investigator must accept that regulatory authorities and sponsor representatives may conduct inspections to verify compliance with GCP guidelines.

12. ETHICS

12.1. Informed Consent

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and/or oral information about the study will be provided in a language as nontechnical as practical and understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study.

Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to the IEC/IRB requirements. The patient's willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original consent forms, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

12.2. Health Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national/local health authorities and to each IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and health authority (where applicable) for the center give written approval or a favorable opinion.

12.3. Confidentiality Regarding Study Patients

Each investigator must assure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification code (eg, initials and identification number).

Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the source and transcribed onto the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

12.4. Declaration of the End of the Clinical Study

For clinical investigational centers located in the EU, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/ED, Article 10(c); for other countries, local regulations will be followed.

12.5. Registration of the Clinical Study

In accordance with sponsor's standard procedures, this clinical study will be registered on clinical trials registry websites, such as clinicaltrials.gov.

13. DATA HANDLING, DATA QUALITY CONTROL, AND RECORD KEEPING

13.1. Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21 CFR part 11. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient screened according to the data source. Patient identity should not be discernible from the data provided on the CRF. Data will be verified using the data source by the study monitor, and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data), the results will be sent to the investigational center where they will be retained but not entered into the CRF unless otherwise specified in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management) for direct entry into the clinical database (see Section 3.9). Laboratory test results will not be entered into the CRF unless otherwise noted in the protocol. All data from other sources will be available to the investigator(s).

For patients who enter a study but do not meet screening criteria, at a minimum, data for screen failure reason, demography, and adverse events from the time of informed consent will be entered into the CRF.

13.2. Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality assurance, will comply with international regulatory guidelines, including ICH GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality assurance, will be described in a data management plan.

Case report forms received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and

accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS. Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS update function. The system requires a reason for each change and keeps a complete audit trail of the data values, dates and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

13.3. Archiving of Case Report Forms and Source Documents

13.3.1. Investigator Responsibilities

All records related to the study (ie, source data, source documents, CRFs [see Section 3.9], data results from other sources [see Section 13.1], copies of protocols and protocol amendments, drug accountability forms, correspondence, patient identification lists, signed informed consent forms, and other essential documents) must be retained until the sponsor notifies the institution, in writing, that records may be destroyed.

If the sponsor has not provided written notification of records destruction after 15 years from study completion (or earlier in the event of an institution closing), and the institution determines the study record retention is unduly burdensome, the institution may submit a written request to the sponsor at least 60 days before the planned disposition of the study records. No study document or image (eg, scan, radiograph, ECG tracing) should be destroyed without prior written agreement between the sponsor and each investigator. Should an investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to the sponsor.

13.3.2. Sponsor Responsibilities

The sponsor will be responsible for the processing and quality control of the data. Data management and filing will be carried out as described in the sponsor's SOPs for clinical studies.

If data management and filing of documents for this study are delegated to a contract organization, these functions will be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management and filing activities. The original CRFs will be archived by the sponsor. Center-specific CRFs will be provided to the respective investigational centers for archiving.

14. FINANCING AND INSURANCE

A separate financial agreement will be made between the principal investigator and the sponsor before the study drug is delivered.

This clinical study is insured in accordance with the corresponding local legal provisions.

The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions.

Excluded from the insurance cover are, inter alia, damages to health and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete Form FDA 3454. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

15. REPORTING AND PUBLICATION OF RESULTS

The sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to local and regional requirements for registration and posting of results.

The sponsor is responsible for preparing a clinical study report, in cooperation with the coordinating investigator. The final report is signed by the sponsor and, if applicable, by the coordinating investigator.

When the sponsor generates reports from the data collected in this study for presentation to regulatory authorities, drafts may be circulated to the coordinating investigator for comments and suggestions. An endorsement of the final report will be sought from the coordinating investigator.

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor. The primary publication from this study will report the results of the study in accordance with the current "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as established by the International Committee of Medical Journal Editors (www.ICMJE.org). Authorship will be restricted to parties who have editorial or conceptual input to protocol design, collection of data and/or analysis, interpretation of data, and manuscript preparation. The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent application(s) based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

16. REFERENCES

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17. SUMMARY OF CHANGES TO PROTOCOL

17.1. Amendment 01 Dated 22 April 2015

The primary reasons for this amendment are 1) the French Competent Authority review of the sponsor's regulatory submission, where they required clarification that patients with the T315I specific mutation should not be enrolled into the 2057 study unless they have failed or were intolerant to ponatinib as one of their prior therapies, assuming they are medically fit to receive this TKI, 2) risk benefit information added in protocol in response to comment from the Central Ethics Committee (CEC) to add risk benefit information, and 3) revised specifics for reporting serious adverse events section and updated relationship categories under assessment of safety based on new protocol template.

The revisions listed below have been made to the protocol (and protocol synopsis, as appropriate) and some are considered substantial by the Teva Authorized Representative. Minor editorial changes have also been made to the protocol, but are not listed in the table below.

Initial wording	Amended or new wording	Reason/Justification for change
Chapter/section concerned: Header Clinical Study Protocol	Chapter/section concerned: Header Clinical Study Protocol ***with Amendment 01***	Added that this is Amendment 01
Chapter/section concerned: Title Page Clinical Study Protocol Protocol Approval Date:	Chapter/section concerned: Title Page Clinical Study Protocol ***with Amendment 01*** Protocol ***Amendment 01*** Approval Date:	Added that this is Amendment 01
Chapter/section concerned: Title Page, Authorized Representative (Signatory) [redacted] Teva Pharmaceuticals	Chapter/section concerned: Title Page, Authorized Representative (Signatory) [redacted] Teva Pharmaceuticals Date of copyright changed from 2012 to 2015.	Change in Administration. Changed date to reflect year the protocol was approved.
Chapter/section concerned: Title Page This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Conference on Harmonization (ICH); United States (US) Code of Federal Regulations (CFR) and European Union (EU) Directives (as applicable in the region of the study); local country regulations; and the sponsor's Standard Operating Procedures (SOPs). This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D, Inc., and its affiliate, Cephalon, Inc. (collectively the "Sponsor"). The recipient agrees that no information contained herein may be published or disclosed without written approval from the Sponsor.	Chapter/section concerned: Title Page ***Confidentiality Statement*** This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Conference on Harmonization (ICH); United States (US) Code of Federal Regulations (CFR) and European Union (EU) Directives (as applicable in the region of the study); local country regulations; and the sponsor's Standard Operating Procedures (SOPs). This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D, Inc., and its affiliate, Cephalon, Inc. (collectively the "Sponsor"). The recipient agrees that no information contained herein may be published or disclosed without written approval from the Sponsor.	The words "Confidentiality Statement" were missing from the title page.

Initial wording	Amended or new wording	Reason/Justification for change
Chapter/section concerned:	Chapter/section concerned: Amendment history page added.	Amendment history page added because we have an administrative letter and Amendment 01 to add.
Chapter/section concerned: Investigator Agreement	Chapter/section concerned: Investigator Agreement Sponsor's Authorized Representative changed from [redacted] to [redacted] and revised Investigator Agreement page inserted.	Updated to reflect revised protocol template and change in administration.
Chapter/section concerned: Coordinating Investigator Agreement (For studies in the EUropean union)	Chapter/section concerned: Coordinating Investigator Agreement (For studies in the EUropean union) This page was deleted because the new Investigator Agreement page replaces the Coordinating Investigator page.	This page was deleted because the new Investigator Agreement page replaces the Coordinating Investigator page.
Chapter/section concerned: CLINICAL STUDY PERSONNEL CONTACT INFORMATION For protocol and clinical questions, contact: [redacted] Teva Pharmaceuticals [redacted] For study operational issues, contact the operational lead listed below: [redacted] Teva Pharmaceuticals [redacted]	Chapter/section concerned: CLINICAL STUDY PERSONNEL CONTACT INFORMATION For protocol and clinical questions, contact: [redacted] Teva Pharmaceuticals [redacted] For study operational issues, contact the operational lead listed below: [redacted] Teva Pharmaceuticals [redacted]	Change in Administration. Correction to fax number for [redacted]
Chapter/section concerned:	Chapter/section concerned:	The protocol was amended as a

Initial wording	Amended or new wording	Reason/Justification for change
Clinical Study Protocol Synopsis Criteria for Inclusion b	Clinical Study Protocol Synopsis Criteria for Inclusion b The following text was added as a bullet point under criteria for exclusion b: • ***Patients with a known T315I mutation must have been treated and failed ponatinib (prior to the entry into this study; this would not apply in a country where ponatinib has not been approved or where patients otherwise would not have access to this medication) unless medically contraindicated by the treating study doctor***	result of the French Competent Authority review of the sponsor's regulatory submission, where they required clarification that patients with this specific mutation should not be enrolled into the 2057 study unless they have failed or were intolerant to ponatinib as one of their prior therapies, assuming they are medically fit to receive this TKI.
Chapter/section concerned: Clinical Study Protocol Synopsis Criteria for Exclusion: b. The patient has had a myocardial infarction in the previous 12 weeks.	Chapter/section concerned: Clinical Study Protocol Synopsis Criteria for Exclusion: b. The patient has had a myocardial infarction in the previous 12 weeks. ***(Prior to study entry, any other electrocardiogram [ECG] abnormalities noted at screening other than myocardial infarction within the previous 12 weeks and felt by the investigator not to be medically relevant, must be documented as such.)***	Clarification.
Chapter/section concerned: Clinical Study Protocol Synopsis Duration of Patient Participation The study will consist of up to a 7-day screening period, and treatment for up to 12 months depending on response and tolerability. Patients will also have an end-of-treatment follow-up visit approximately 28 days after the last dose of omacetaxine.	Chapter/section concerned: Clinical Study Protocol Synopsis Duration of Patient Participation The study will consist of up to a 7-day screening period, and treatment for up to 12 months depending on response and tolerability. Patients will also have an end-of-treatment follow-up visit approximately 28 days ***(+2 days)*** after the last dose of omacetaxine.	Added +2 days so there is a window of 3 days for the visit to occur and can cover over a weekend or a holiday.
Chapter/section concerned: Clinical Study Protocol Synopsis General Design and Methodology: In both phases, omacetaxine will be administered by subcutaneous injection twice daily. For cycle 1, the first dose will be administered at the investigational center. Subsequent doses (in prefilled syringes) may be administered on an outpatient basis after training takes place. Patients will be evaluated every 7 days with complete blood and platelet counts up to and including cycle 5 and every 2 weeks after cycle 5; the number of	Chapter/section concerned: Clinical Study Protocol Synopsis General Design and Methodology: In both phases, omacetaxine will be administered by subcutaneous injection twice daily. For cycle 1, the first dose will be administered at the investigational center. Subsequent doses (in prefilled syringes) may be administered on an outpatient basis after training takes place. Patients will be evaluated every 7 days with complete blood and platelet counts up to and including cycle 5 and every 2 weeks ***(±2 days)*** after cycle 5; the number of consecutive doses of omacetaxine or intervals between subsequent	All chemistry and hematology tests have a ±2 day window. Clarification of every 3 months. Text added for consistency between sections of protocol.

Initial wording	Amended or new wording	Reason/Justification for change
consecutive doses of omacetaxine or intervals between subsequent cycles may be adjusted, as clinically indicated. Every 3 months, bone marrow aspiration and cytogenetics, BCR-ABL transcript measurements, quantitative BCR-ABL kinase domain analysis of peripheral blood, and ECGs will be performed.	cycles may be adjusted, as clinically indicated. Every 3 months ***(ie, every 3 cycles)***, bone marrow aspiration and cytogenetics, BCR-ABL transcript measurements, quantitative BCR-ABL kinase domain analysis of peripheral blood, and ECGs will be performed. ***Note: After a patient achieves a confirmed complete cytogenetic response, RT-PCR BCR-ABL testing should be performed every 6 months unless clinically indicated to do it more often.***	
Chapter/section concerned: Clinical Study Protocol Synopsis Pharmacokinetics: • 1ne sample on day 13, 14, 15, 16, or 17 either predose 1 or predose 2 • 1one sample either predose 1 or predose 2 on any day during wee21	Chapter/section concerned: Clinical Study Protocol Synopsis Pharmacokinetics: • 1~~***ne***~~ sample on day 13, 14, 15, 16, or 17 either predose 1 or predose 2 • 1~~***one***~~ sample either predose 1 or predose 2 on any day during ~~***wee21***~~ week 2	Correction of typographical errors.
Chapter/section concerned: List of abbreviations and definitions of terms	Chapter/section concerned: List of abbreviations and definitions of terms ***CEC, Central Ethics Committee ~~Commission of the European Communities~~, abbreviation added.*** ***CO2, carbon dioxide, abbreviation added.*** ***PPD, Pharmaceutical Product Development, LLC, abbreviation added.*** ***RR, respiratory rate, abbreviation added.*** ***XML, extensible markup language, abbreviation added.***	New abbreviations added.
Chapter/section concerned: 1.1.3 Rationale for the Study In oncology, the dosage of nearly all cytotoxic drugs is based on body-surface area (BSA) of the patient (Field et al 2008, Mathijssen et al 2007). However, fixed or "flat dosing", using a single dose for all patients regardless of BSA or weight may offer advantages with regard to administration errors and patient safety for a drug given subcutaneously. To satisfy a postmarketing requirement (PMR), the sponsor has been requested to conduct a Phase 1/Phase 2 single-group clinical study to investigate the pharmacokinetics and preliminary safety and efficacy of omacetaxine following a fixed-dose administration to patients with CP or AP	Chapter/section concerned: 1.1.3 Rationale for the Study In oncology, the dosage of nearly all cytotoxic drugs is based on body-surface area (BSA) of the patient (Field et al 2008, Mathijssen et al 2007). However, fixed or "flat dosing", using a single dose for all patients regardless of BSA or weight may offer advantages with regard to administration ***dose*** errors and patient safety for a drug given subcutaneously. To satisfy a postmarketing requirement (PMR), the sponsor has been requested ***by FDA*** to conduct a Phase 1/Phase 2 ~~single-group~~ ***open label*** clinical study to investigate the pharmacokinetics and preliminary safety and efficacy of omacetaxine following a fixed-dose administration to patients with CP or AP CML who have failed 2 or more TKI therapies. ***Therefore, this study was designed for the same patient***	Risk benefit information added in protocol in response to comment from CEC to add risk benefit information. Editorial changes.

Initial wording	Amended or new wording	Reason/Justification for change
CML who have failed 2 or more TKI therapies. A population pharmacokinetic model was developed for omacetaxine using the pharmacokinetic data collected in Study CGX-635-205 and it was used to predict individual measures of omacetaxine exposure in patients enrolled in Studies CGX-635-202 and CGX-635-203, respectively. Study CGX-635-205 assessed pharmacokinetics and safety of subcutaneous omacetaxine in patients with advanced cancers, and had results recently published (Nemunaitis et al 2013). The relationships between these individual exposure estimates and efficacy and selected safety endpoints were investigated. These exposure-response relationships were used to simulate anticipated outcomes, with data from the CML registration Studies CGX-635-202 and CGX-635-2032, respectively, with various fixed treatment regimens. The registration studies did not have pharmacokinetics in their study design. A comparison of fixed-doses between 2 and 3.5 mg, without regard to BSA, illustrates that there is potential benefit in terms of an increased predicted probability of efficacy with a dose of 2.5 mg over a 2-mg dose (almost 3-fold increase in the predicted probability of major hematologic response [MaHR] and almost 2-fold increase in the predicted probability of major cytogenic response [MCyR]) (data on file). The 3-mg dose is associated with an even greater predicted probability of efficacy in both the AP and CP populations. The increased risk associated with these doses, in terms of the predicted probability of experiencing grade 3 or grade 4 thrombocytopenia, over the 2-mg dose, is small on the basis of the simulation data, but not fully understood due to the limited size of the CGX-635-205 dataset. The 3.5-mg dose, which represents a higher dose than any administered in Studies CGX-635-205, CGX-635-CML-202, or CGX-635-CML-203, is predicted to provide only a small additional	***population for which omacetaxine was approved but with a "fixed or flat" dosing approach. If this approach proves safe and efficacious as in the registration trials, this would prove to be a benefit to patients and healthcare providers to ensure or avoid less dosing errors when given subcutaneously and improve patient compliance due to improved ease of administration. Additionally, this study was requested since the pharmacokinetics of omacetaxine may or may not be related to BSA. A BSA-based dose could result in lower drug concentrations and potentially reduced efficacy in patients with traditionally lower BSAs, such as women, as women have lower body surface areas. Lower exposures may contribute to reported observations of a lower response rate in women. Therefore, a fixed dose may increase exposure in any patients with low BSA and potentially optimize their probability of response. This PMR study may assist to optimize the dosing regimen in future trials.*** A population pharmacokinetic model was developed for omacetaxine using the pharmacokinetic data collected in Study CGX-635-205 and it was used to predict individual measures of omacetaxine exposure in patients enrolled in Studies CGX-635-202 and CGX-635-203, respectively. Study CGX-635-205 assessed pharmacokinetics and safety of subcutaneous omacetaxine in patients with advanced cancers, and had results recently published (Nemunaitis et al 2013). The relationships between these individual exposure estimates and efficacy and selected safety endpoints were investigated. These exposure-response relationships were used to simulate anticipated outcomes, with data from the CML registration Studies CGX-635-202 and CGX-635-203~~2~~, respectively, with various fixed treatment regimens. The registration studies did not have pharmacokinetics in their study design. A comparison of fixed-doses between 2 and 3.5 mg, without regard to BSA, illustrates that there is potential benefit in terms of an increased predicted probability of efficacy with a dose of 2.5 mg over a ***2 mg*** dose (almost 3-fold increase in the predicted probability of major hematologic response [MaHR] and almost 2-fold increase in the predicted probability of major cytogenic response [MCyR]) (data on file). The ***3 mg*** dose is associated with an even greater predicted probability of efficacy in both the AP	

Initial wording	Amended or new wording	Reason/Justification for change
improvement in the probability of efficacy and in the risk of neutropenia over the 3-mg alternative, and also a slightly increased risk of thrombocytopenia over the 3-mg alternative; and it comes with the added uncertainty of being outside the range of previously tested doses. Therefore, administration of this dose is not recommended. Because the number of patients in Study CGX-635-205 was small, the predictions from this population pharmacokinetic modeling must be used with caution. On the basis of the data currently available, the impact of fixed dose on the benefit-risk profile in patients with CML who have failed TKI therapy remains unknown. For this reason, a fixed dose of 2.5 mg twice daily was selected because it approximates to the dose that would have been given to a patient of median BSA under the current 1.25 mg/m^2 twice daily regimen. A sample size of approximately 21 patients enrolled in cohorts of small, medium, and large BSA is considered sufficient to properly characterize the pharmacokinetics of the 2.5 mg twice daily fixed dose.	and CP populations. The increased risk associated with these doses, in terms of the predicted probability of experiencing grade 3 or grade 4 thrombocytopenia, over the ***2 mg*** dose, is small on the basis of the simulation data, but not fully understood due to the limited size of the CGX-635-205 dataset. The ***3.5 mg*** dose, which represents a higher dose than any administered in Studies CGX-635-205, CGX-635-CML-202, or CGX-635-CML-203, is predicted to provide only a small additional improvement in the probability of efficacy and in the risk of neutropenia over the ***3 mg*** alternative, and also a slightly increased risk of thrombocytopenia over the ***3 mg*** alternative; and it comes with the added uncertainty of being outside the range of previously tested doses. Therefore, administration of this dose is not recommended. Because the number of patients in Study CGX-635-205 was small, the predictions from this population pharmacokinetic modeling must be used with caution. On the basis of the data currently available, the impact of fixed dose on the benefit-risk profile in patients with CML who have failed TKI therapy remains unknown. For this reason, a fixed dose of 2.5 mg twice daily was selected because it approximates to the dose that would have been given to a patient of median BSA under the current 1.25 mg/m^2 twice daily regimen. ***In the phase 1 portion of the study, a*** ~~A~~ sample size of approximately 21 patients enrolled in cohorts of small, medium, and large BSA is considered sufficient to properly characterize the pharmacokinetics of the 2.5 mg twice daily fixed dose.	
Chapter/section concerned: 1.3.5 Justification for Study Treatment Plan The purpose of this current study is to evaluate the pharmacokinetics and the preliminary safety and efficacy of a fixed-dose regimen of omacetaxine for the treatment of patients with CP or AP CML following failure of TKI therapy. For this reason the treatment plan is the same as that used in the Phase 2 registration studies for omacetaxine (Studies CGX-635-CML-202 and CGX-635-CML-203) with a fixed dose being used in place of doses adjusted for BSA. Stopping rules and	Chapter/section concerned: 1.3.5 Justification for Study Treatment Plan The purpose of this current study is to evaluate the pharmacokinetics and the preliminary safety and efficacy of a fixed-dose regimen of omacetaxine ***(2.5 mg BID sc)*** for the treatment of patients with CP or AP CML following failure of TKI therapy. For this reason, the treatment plan is the same as that used in the Phase 2 registration studies for omacetaxine (Studies CGX-635-CML-202 and CGX-635-CML-203) with a fixed dose being used in place of doses adjusted for BSA ***and with the***	Risk benefit information added in protocol in response to comment from CEC to add risk benefit information.

Initial wording	Amended or new wording	Reason/Justification for change
an independent DMC that will evaluate safety, pharmacokinetics, and efficacy, will be implemented, as defined in its charter. The treatment plan includes recommendations for alternative therapies and management of toxicities, including hematologic toxicity, if necessary.	***precautions to minimize toxicity and improve tolerability as described in Section 1.4 called Known and Potential Risks and Benefits to Human Patients. As an additional precaution for unforeseeable risks, an independent DMC that will evaluate safety, pharmacokinetics, and efficacy, has been implemented from the beginning of the study including the phase 1 portion as defined in its charter.*** ~~Stopping rules and an independent DMC that will evaluate safety, pharmacokinetics, and efficacy, will be implemented, as defined in its charter.~~ ***The study treatment plan includes recommendations for supportive therapies and management of toxicities, including hematologic toxicity, if necessary. Refer please, to*** *Section 3* ***and*** *Section 5* ***of the protocol CEP 41443/2057 for full details.*** ~~The treatment plan includes recommendations for alternative therapies and management of toxicities, including hematologic toxicity, if necessary.~~	
Chapter/section concerned: 3.1 General Design and Study Schema The study will consist of up to a 7-day screening period, and treatment for up to 12 months, in Phase 1 and Phase 2 portions, depending on response and tolerability. Patients will also have an end-of-treatment follow-up visit approximately 28 days after the last dose of omacetaxine.	Chapter/section concerned: 3.1 General Design and Study Schema The study will consist of up to a 7-day screening period, and treatment for up to 12 months, in Phase 1 and Phase 2 portions, depending on response and tolerability. Patients will also have an end-of-treatment follow-up visit approximately 28 days ***(+2 days)*** after the last dose of omacetaxine.	Added +2 days so there is a window of 3 days for the visit to occur and can cover over a weekend or a holiday.
Chapter/section concerned: 3.1 General Design and Study Schema **Phase 1 and Phase 2:** Omacetaxine will be administered by subcutaneous injection twice daily. For cycle 1, the first dose will be administered at the investigational center. Subsequent doses (in prefilled syringes) may be administered on an outpatient basis after training takes place. See Section 5.1.1 regarding training for the patient or caregiver for administration of omacetaxine. Patients will be evaluated every 7 days with complete blood and platelet counts up to and including cycle 5, and every 2 weeks after cycle 5 (see Section 3.11.2.5); the number of consecutive doses of omacetaxine or intervals between subsequent cycles may be adjusted,	Chapter/section concerned: 3.1 General Design and Study Schema **Phase 1 and Phase 2:** Omacetaxine will be administered by subcutaneous injection twice daily. For cycle 1, the first dose will be administered at the investigational center. Subsequent doses (in prefilled syringes) may be administered on an outpatient basis after training takes place. See Section 5.1.1 regarding training for the patient or caregiver for administration of omacetaxine. Patients will be evaluated every 7 days with complete blood and platelet counts up to and including cycle 5, and every 2 weeks ***(±2 days)*** after cycle 5 (see Section 3.11.2.5); the number of consecutive doses of omacetaxine or intervals between subsequent cycles may be adjusted, as clinically indicated, according to guidelines provided in Section 5.1.2. The following tests will be performed every 3 months ***(ie, every 3***	All chemistry and hematology tests have a ±2 day window. Clarification of every 3 months. Added text about 12 months for consistency between sections. Clarification of BCR-ABL testing so that it is more specific.

Initial wording	Amended or new wording	Reason/Justification for change
as clinically indicated, according to guidelines provided in Section 5.1.2. The following tests will be performed every 3 months while on study, for all patients: • bone marrow aspiration and cytogenetics every 3 months If patients show other clinical signs of disease progression they may not need to undergo a bone marrow evaluation. The treatment cycle following a bone marrow procedure for the long-term responders may begin up to 7 (±3) days after the bone marrow procedure. Cytogenetic response evaluation will be based on standard cytogenetic analysis (at least 20 metaphases are to be analyzed). Note: After a patient achieves a confirmed cytogenetic response, bone marrow aspiration with cytogenetics will be performed every 12 months or as often as clinically indicated. At this stage, chromosome banding analysis of marrow cell metaphases (with at least 20 metaphases analyzed) can be substituted by florescence in situ hybridization (FISH) on blood cells once a complete cytogenetic response has been confirmed (Baccarani et al 2013, SYNRIBO prescribing information). • measure BCR-ABL transcript levels by real-time, quantitative polymerase chain reaction (PCR) of peripheral blood performed locally Note: After a patient achieves a confirmed complete cytogenetic response, this test should be performed every 6 months unless clinically indicated to do it more often (Appendix A).	***cycles)*** while on study, for all patients: • bone marrow aspiration and cytogenetics every 3 months If patients show other clinical signs of disease progression they may not need to undergo a bone marrow evaluation. The treatment cycle following a bone marrow procedure for the long-term responders may begin up to 7 (±3) days after the bone marrow procedure. Cytogenetic response evaluation will be based on standard cytogenetic analysis (at least 20 metaphases are to be analyzed). Note: After a patient achieves a confirmed cytogenetic response, bone marrow aspiration with cytogenetics will be performed every 12 months or as often as clinically indicated. At this stage, ***after the patient has been on study for at least 12 months,*** chromosome banding analysis of marrow cell metaphases (with at least 20 metaphases analyzed) can be substituted by florescence in situ hybridization (FISH) on blood cells once a complete cytogenetic response has been confirmed (Baccarani et al 2013, SYNRIBO prescribing information). • measure BCR-ABL transcript levels by real-time, quantitative polymerase chain reaction (PCR) of peripheral blood performed locally Note: After a patient achieves a confirmed complete cytogenetic response, ~~this test~~ ***RT-PCR BCR-ABL testing*** should be performed every 6 months unless clinically indicated to do it more often (Appendix A).	
Chapter/section concerned: 3.2.2 Secondary Efficacy Measures and Endpoints • molecular response by site (peripheral transcript of BCR-ABL) (Appendix A) assessed every 3 months	Chapter/section concerned: 3.2.2 Secondary Efficacy Measures and Endpoints • molecular response by site (peripheral transcript of BCR-ABL) (~~Appendix A~~ ***Appendix B***) assessed every 3 months ***(ie, every 3 cycles)***	Clarification of every 3 months. Correction of Appendix.
Chapter/section concerned:	Chapter/section concerned:	Correction to vial size.

Initial wording	Amended or new wording	Reason/Justification for change
3.4.1 Investigational Product and Dosage The investigational drug for this study is omacetaxine mepesuccinate. Omacetaxine drug product is a lyophilized vial containing 3.5 mg omacetaxine and 10 mg mannitol in a 10-mL clear glass vial, sealed with rubber stopper and aluminum flip-off seal. Investigational centers will be given vials of 3.5 mg omacetaxine. Omacetaxine will be reconstituted by a healthcare professional.	3.4.1 Investigational Product and Dosage The investigational drug for this study is omacetaxine mepesuccinate. Omacetaxine drug product is a lyophilized vial containing 3.5 mg omacetaxine and 10 mg mannitol in a**n 8**~~10~~-mL clear glass vial, sealed with rubber stopper and aluminum flip-off seal. Investigational centers will be given vials of 3.5 mg omacetaxine. Omacetaxine will be reconstituted by a healthcare professional.	
Chapter/section concerned: 3.5 Duration of Patient Participation The study will consist of up to a 7-day screening period, and treatment for up to 12 months depending on response and tolerability. Patients will also have an end-of-treatment follow-up visit approximately 28 days after the last dose of omacetaxine.	Chapter/section concerned: 3.5 Duration of Patient Participation The study will consist of up to a 7-day screening period, and treatment for up to 12 months depending on response and tolerability. Patients will also have an end-of-treatment follow-up visit approximately 28 days ***(+2 days)*** after the last dose of omacetaxine.	Added +2 days so there is a window of 3 days for the visit to occur and can cover over a weekend or a holiday.
Chapter/section concerned: 3.7.1 Study Drug Storage and Security Table 1: Time to Administration After Reconstitution Within 24 hours of reconstitution	Chapter/section concerned: 3.7.1 Study Drug Storage and Security Table 1: Time to Administration After Reconstitution Within ~~24 hours~~ ***6 days (144 hours)*** of reconstitution	Revised storage duration.
Chapter/section concerned: 3.7.2 Study Drug Accountability For every cycle, the first dose will be reconstituted by the healthcare professional and administered at the investigational center.	Chapter/section concerned: 3.7.2 Study Drug Accountability ~~For every cycle, the first dose will be reconstituted by the healthcare professional and administered at the investigational center.~~ ***For the first cycle, the first dose will be reconstituted by the healthcare professional and administered at the investigational center. For any additional cycles, the first dose may be administered at the investigational center by a healthcare professional, self-administered at home by the patient, or administered by the Sponsor selected home care agency professional at the home of the patient.***	Added information that is optional for the patient to have their first dose of cycles after C1 to be administered in the clinic, regardless of whether it is by a healthcare professional or self-administered by the patient. Clarification that additional cycles after the first dose may be administered at home.
Chapter/section concerned: 3.10 Time Schedule The study is expected to start enrolling in approximately the second quarter of 2014 and be completed enrollment approximately in 2016. The study is planned to be conducted at approximately 40	Chapter/section concerned: 3.10 Time Schedule The study is expected to start enrolling in approximately the second quarter of 2014 and be completed enrollment approximately in 2016. The study is planned to be conducted at approximately ***24*** ~~40~~ study centers in North America***, Europe, and***	Correction to number of study centers and countries where study will be conducted.

Initial wording	Amended or new wording	Reason/Justification for change
study centers in North America and the EU.	***Asia*** ~~and the EU~~.	
Chapter/section concerned: 3.11 Study Procedures Table 2, Header Omacetaxine induction or maintenance treatment 28-day cycles (up to 12 cycles total)	Chapter/section concerned: 3.11 Study Procedures Table 2, Header Omacetaxine induction or maintenance treatment 28-day cycles ***(±1 day)***(up to 12 cycles total)	Added window of ±1 day
Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes [b]Follow-up every 3 months; the first visit will be in person but the rest may be by telephone contact. Follow-up will continue until patient's death or 12 months after the last treatment cycle, whichever occurs first. Follow-up is required even if a patient is withdrawn from treatment with omacetaxine.	Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes [b]Follow-up ***visits*** every 3 months ***(±7 days)***; the first visit will be in person but the rest may be by telephone contact. Follow-up will continue until patient's death***, is lost to follow-up,*** or ***until*** 12 months after the last treatment cycle, whichever occurs first***, regardless of receiving other anticancer treatment.*** Follow-up is required even if a patient is withdrawn from treatment with omacetaxine.	Added window of ±7 days for follow-up visits. Added text for consistency between sections
Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes [e]If a patient completes treatment with omacetaxine or is withdrawn from treatment, assessments will be performed at an end-of-treatment visit 28 days after the last dose of study drug. If the patient is withdrawn from treatment, an end-of-treatment visit may occur before 28 days after the last dose of omacetaxine to allow the patient to enter follow-up.	Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes [e]If a patient completes treatment with omacetaxine or is withdrawn from treatment, assessments will be performed at an end-of-treatment visit 28 days ***(+2 days)*** after the last dose of study drug. If the patient is withdrawn from treatment, an end-of-treatment visit may occur before 28 days after the last dose of omacetaxine to allow the patient to enter follow-up.	Added +2 days so there is a window of 3 days for the visit to occur and can cover over a weekend or a holiday.
Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes [i]Measure vital signs (HR, BP, temperature) within 30 minutes prior to administration of omacetaxine and 20 minutes after administration on day 1 of each treatment cycle.	Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes [i]Measure vital signs (HR, BP, **RR**, ~~***temperature***~~ ***T***) within 30 minutes prior to administration of omacetaxine and 20 minutes ***post-dose (±5 min)*** ~~after administration~~ on day 1 of each treatment cycle.	Added RR and window of ±5 min post dose for vital signs. Changed temperature to T abbreviation for consistency.
Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes j May be omitted if prior study available within preceding 30 days.	Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes j ~~***May be omitted if prior study available within preceding 30 days.***~~ ***Chest x-ray may be omitted if a prior study, such as a CT of the chest, is completed within 30 days of first dose of***	Revised for clarity.

Initial wording	Amended or new wording	Reason/Justification for change
	omacetaxine. A screening bone marrow or ECG is required only if a prior one has not been performed within 30 days of first dose of omacetaxine.	
Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes k Prior to the first 3 cycles (cycles 1 through 3) whether induction or maintenance. It may be omitted at cycle 1 if one was done within 30 days prior to the first dose of omacetaxine on day 1 of cycle 1). In other countries, electrocardiograms may be done before and after every omacetaxine cycle, or as directed.	Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes k Prior to the first 3 cycles (cycles 1 through 3) whether induction or maintenance. It may be omitted at cycle 1 if one was done within 30 days prior to the first dose of omacetaxine on day 1 of cycle 1). In other countries, ~~electrocardiograms~~ ***ECGs*** may be done before and after every omacetaxine cycle, or as directed.	Abbreviation for ECG added.
Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes [m]Complete blood counts to include hematocrit, hemoglobin, RBC, WBC, differential, platelet count.	Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes [m]Complete blood counts ***(±2 days)*** to include hematocrit, hemoglobin, RBC, WBC, differential, platelet count.	Added window of ±2 days for hematology.
Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes [o]Full serum chemistry and hematology to be performed every 2 weeks after cycle 5.	Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes [o]Full serum chemistry and hematology to be performed every 2 weeks ***(±2 days)*** after cycle 5.	All chemistry and hematology tests have a ±2 day window.
Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes p Full serum chemistry to be performed at screening and after cycle 5. During cycles 1 through 5, chem 7 (sodium, chloride, CO2, creatinine, BUN or urea, glucose, and potassium) is to be performed.	Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes p Full serum chemistry to be performed at screening and after cycle 5. During cycles 1 through 5, chem 7 (sodium, chloride, CO2 ***content***, creatinine, BUN or urea, glucose, and potassium) is to be performed.	Added for consistency within the protocol.
Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes [q]Bone marrow exam with cytogenetic analysis to be performed by the G-banding technique. Marrow specimens will be examined on direct short-term (24-hour) cultures; at least 20 metaphases are to be analyzed. May be omitted at screening if bone marrow and cytogenetic analysis have been done in the preceding 30 days and the patient had not received	Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes [q]Bone marrow exam with cytogenetic analysis to be performed by the G-banding technique. Marrow specimens will be examined on direct short-term (24-hour) cultures; at least 20 metaphases are to be analyzed. May be omitted at screening if bone marrow and cytogenetic analysis have been done in the preceding 30 days and the patient had not received antileukemic therapy during this period (other than palliative therapy, eg, hydroxyurea). ***After 12***	Added for consistency with section 3.1

Initial wording	Amended or new wording	Reason/Justification for change
antileukemic therapy during this period (other than palliative therapy, eg, hydroxyurea).	***months on study, and once a complete cytogenetic response has been confirmed, may substitute chromosome banding analysis with FISH on blood cells.***	
Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes t Obtain BCR-ABL quantitative transcript levels by quantitative PCR analysis of peripheral blood. BCR-ABL transcripts will be detected by real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis on peripheral blood.	Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes t Obtain BCR-ABL quantitative transcript levels by quantitative PCR analysis of peripheral blood. BCR-ABL transcripts will be detected by real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis on peripheral blood. ***After a patient achieves a confirmed complete cytogenetic response, this test should be performed every 6 months unless clinically indicated to do it more often.***	Added for consistency within the protocol.
Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes HR=heart rate; RR=respiratory rate; BP=blood pressure; T=temperature; RBC=red blood cell; WBC=white blood cell; BUN=blood urea nitrogen; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; PCR=polymerase chain reaction; CML=chronic myeloid leukemia.	Chapter/section concerned: 3.11 Study Procedures Table 2, Footnotes HR=heart rate; RR=respiratory rate; BP=blood pressure; T=temperature; RBC=red blood cell; WBC=white blood cell; BUN=blood urea nitrogen; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; PCR=polymerase chain reaction; CML=chronic myeloid leukemia***., CO2=carbon dioxide, FISH=florescence in situ hybridization.***	Added abbreviations used in table.
Chapter/section concerned: 3.11 Study Procedures Table 3, Footnotes [b]Pharmacokinetic samples to be drawn once, either on day 10 or day 11 or day 12.	Chapter/section concerned: 3.11 Study Procedures Table 3, Footnotes [b]Pharmacokinetic samples to be drawn once, either on day 10 or ~~***day***~~ 11 or ~~***day***~~ 12. ***Day 10 or 11 or 12, <1 hr sample and 1-12 hr sample should be drawn at least 30 minutes apart.***	To clarify samples should be drawn with sufficient time between each collection on Day 10 or 11 or 12. Editorial change for consistency.
Chapter/section concerned: 3.11 Study Procedures Table 4, Footnotes After day 1 during week 1 Any day during week 2	Chapter/section concerned: 3.11 Study Procedures Table 4, Footnotes Footnote b was added After day 1 during week 1***[b]*** Any day during week 2 ***[b]*** ***[b] Day 10 or 11 or 12, <1 hr sample and 1-12 hr sample should be drawn at least 30 minutes apart.***	To clarify samples should be drawn with sufficient time between each collection on Day 10 or 11 or 12.
Chapter/section concerned: 3.11 Study Procedures Table 4, Footnotes	Chapter/section concerned: 3.11 Study Procedures Table 4, Footnotes	Deleted abbreviation that wasn't used and added new abbreviation.

Initial wording	Amended or new wording	Reason/Justification for change
min=minutes; hr=hour; NA=not applicable.	~~min=minutes~~ ***bid=twice daily***; hr=hour; NA=not applicable.	
Chapter/section concerned: 3.11.1 Procedures for Screening and Enrollment • ECG, unless one was performed within the preceding 30 days.	Chapter/section concerned: 3.11 Procedures for Screening and Enrollment • ECG, unless one was performed within the preceding 30 days. ***Prior to study entry, any other ECG abnormalities noted at screening other than myocardial infarction within the previous 12 weeks and felt by the investigator not to be medically relevant, must be documented as such.***	Clarification
Chapter/section concerned: 3.11.2.1 Procedures for Day 1 of Each Treatment Cycle • vital signs (temperature, heart rate, respiratory rate, systolic and diastolic blood pressure) within 30 minutes before omacetaxine and 20 minutes post-injection on day 1 of each treatment cycle • serum chemistry 7 (sodium, chloride, CO_2 content, creatinine, blood urea nitrogen (BUN) or urea, blood glucose, and potassium only) (Appendix D)	Chapter/section concerned: 3.11.2.1 Procedures for Day 1 of Each Treatment Cycle • vital signs (temperature, heart rate, respiratory rate, systolic and diastolic blood pressure) within 30 minutes before omacetaxine and 20 minutes post-injection ***(±5 min)*** on day 1 of each treatment cycle • serum chemistry 7 (sodium, chloride, ***carbon dioxide [CO_2]*** content, creatinine, blood urea nitrogen (BUN) or urea, blood glucose, and potassium only) (Appendix D) • ***Review of updated patient diaries and inquiries on compliance of omacetaxine administration. Please refer to the Patient Instructions on Subcutaneous Injection and Diary Completion for further details.***	Added window of ±5 min post dose for vital signs. Added definition for CO2 abbreviation. Added information about review of patient diaries and compliance for consistency between protocol sections.
Chapter/section concerned: 3.11.2.2 Pharmacokinetic Procedures, Phase 1, Cycle 1 Only • On day 10 or 11 or 12, as follows: – predose, within (<) 1 hour after dose 1, and 1 to 12 hours after dose 1	Chapter/section concerned: 3.11.2.2 Pharmacokinetic Procedures, Phase 1, Cycle 1 Only • On day 10 or 11 or 12, as follows: – predose, within (<) 1 hour after dose 1, and 1 to 12 hours after dose 1 – ***<1 hr sample and 1-12 hr sample should be drawn at least 30 minutes apart.***	To clarify samples should be drawn with sufficient time between each collection on Day 10 or 11 or 12.
Chapter/section concerned: 3.11.2.3 Pharmacokinetic Procedures, Phase 1, Cycles 2 and 3 and Phase 2, Cycles 1 Through 3 Blood samples (2.5 mL) will be obtained in Phase 1 on day 1 of cycles 2 and 3 as follows (see Table 4): • within (<) 1 hour after dose 1	Chapter/section concerned: 3.11.2.3 Pharmacokinetic Procedures, Phase 1, Cycles 2 and 3 and Phase 2, Cycles 1 Through 3 Blood samples (2.5 mL) will be obtained in Phase 1 on day 1 of cycles 2 and 3 as follows (see Table 4): • within (<) 1 hour after dose 1	Correction of typo, “e” deleted. To clarify samples should be drawn with sufficient time between each collection on Day 10 or 11 or 12.

Initial wording	Amended or new wording	Reason/Justification for change
• 1 to 12 hours after dose 1 • 1 sample either predose 1 or predose 2 on any day after day 1 during week 1 • 1e sample either predose 1 or predose 2 on any day during week 2 Blood samples (2.5 mL) will be obtained in Phase 2 on day 1 of cycles 1, 2 and 3 as follows (see Table 4): • within (<) 1 hour after dose 1 • 1 to 12 hours after dose 1 • 1 sample either predose 1 or predose 2 on any day after day 1 during week 1 • 1 sample either predose 1 or predose 2 on any day during week 2	• 1 to 12 hours after dose 1 • 1 sample either predose 1 or predose 2 on any day after day 1 during week 1 • 1~~e~~ sample either predose 1 or predose 2 on any day during week 2 Blood samples (2.5 mL) will be obtained in Phase 2 on day 1 of cycles 1, 2 and 3 as follows (see Table 4): • within (<) 1 hour after dose 1 • 1 to 12 hours after dose 1 • 1 sample either predose 1 or predose 2 on any day after day 1 during week 1 • 1 sample either predose 1 or predose 2 on any day during week 2 ***On Day 10 or 11 or 12, the <1 hr sample and 1-12 hr sample should be drawn at least 30 minutes apart.***	
Chapter/section concerned: 3.11.2.5 Procedures After Cycle 5 of Treatment The following assessments will be performed on day 14 (versus weekly) for all treatment cycles after cycle 5. • review of completed patient diaries and inquiries on compliance of omacetaxine administration and supplies needed (ie, spill kits, gloves, or biohazard containers)	Chapter/section concerned: 3.11.2.5 Procedures After Cycle 5 of Treatment The following assessments will be performed on day 14 ***(±2 days)*** (versus weekly) for all treatment cycles after cycle 5. • ~~review of completed patient diaries and inquiries on compliance of omacetaxine administration and supplies needed (ie, spill kits, gloves, or biohazard containers)~~ ***review of updated patient diaries and inquiries on compliance of omacetaxine administration***	All chemistry and hematology tests have a ±2 day window. Revised text about patient diaries and compliance for consistency between sections.
Chapter/section concerned: 3.11.2.6 Procedures During Study Drug Treatment–Every 3 Months on Study–All Patients The following studies will be obtained every 3 months while on study, in all patients, unless otherwise specified:	Chapter/section concerned: 3.11.2.6 Procedures During Study Drug Treatment–Every 3 Months ***(ie, every 3 cycles)*** on Study–All Patients The following studies will be obtained every 3 months ***(ie, every 3 cycles)*** while on study, in all patients, unless otherwise specified: • ***drug accountability*** • ***adverse event inquiry*** • ***concomitant medication inquiry*** • ***review of updated patient diaries and inquiries on compliance of omacetaxine administration***	Clarification of every 3 months. Additional text added for consistency.

Initial wording	Amended or new wording	Reason/Justification for change
Chapter/section concerned: 3.11.3.1 End-of-Treatment Visit The following procedures will be performed at the end-of-treatment visit, 28 days after the last dose of study drug, unless otherwise specified: • BCR-ABL transcript levels by quantitative PCR of peripheral blood at local laboratory (Appendix B) – may be omitted if prior study within 14 days For patients who complete the study, or for those who withdraw prematurely from the study, final evaluations will be performed 28 days after the last dose of study drug.	Chapter/section concerned: 3.11.3.1 End-of-Treatment Visit The following procedures will be performed at the end-of-treatment visit, 28 days ***(+2 days)*** after the last dose of study drug, unless otherwise specified: • BCR-ABL transcript levels by quantitative PCR of peripheral blood at local laboratory (Appendix B) – ~~may be omitted if prior study within 14 days~~ For patients who complete the study, or for those who withdraw prematurely from the study, final evaluations will be performed 28 days ***(+2 days)*** after the last dose of study drug.	Added +2 days so there is a window of 3 days for the visit to occur and can cover over a weekend or a holiday. Correction of text; statement applied only to the screening BCR-ABL test
Chapter/section concerned: 3.11.3.2 Follow-up Patients will be monitored every 3 months for progression (if the patient had not progressed at the time of the end-of-treatment visit) and survival for 1 year after the last dose of omacetaxine, death, or lost to follow-up, whichever comes first, regardless of patients receiving other anticancer treatment.	Chapter/section concerned: 3.11.3.2 Follow-up Patients will be monitored every 3 months ***(±7 days)*** for progression (if the patient had not progressed at the time of the end-of-treatment visit) and survival for 1 year after the last dose of omacetaxine, death, or lost to follow-up, whichever comes first, regardless of patients receiving other anticancer treatment.	Added window of ±7 days for follow-up visits.
Chapter/section concerned: 4. Selection and Withdrawal of Patients	Chapter/section concerned: 4. Selection and Withdrawal of Patients ***Changes to inclusion and exclusion criteria are indicated below and detailed in Section 17.***	Added sentence that inclusion and exclusion criteria changed.
Chapter/section concerned: 4.1 Patient Inclusion Criteria	Chapter/section concerned: 4.1 Patient Inclusion Criteria Addition of inclusion criterion under b: • ***Patients with a known T315I mutation must have been treated and failed ponatinib (prior to the entry into this study; this would not apply in a country where ponatinib has not been approved or where patients otherwise would not have access to this medication) unless medically contraindicated by the treating study doctor.***	The protocol was amended as a result of the French Competent Authority review of the sponsor's regulatory submission, where they required clarification that patients with this specific mutation should not be enrolled into the 2057 study unless they have failed or were intolerant to ponatinib as one of their prior therapies, assuming they are medically fit to receive this TKI.
Chapter/section concerned: 4.2 Patient Exclusion Criteria	Chapter/section concerned: 4.2 Patient Exclusion Criteria	Clarification and text revised for consistency between sections of

Initial wording	Amended or new wording	Reason/Justification for change
b. The patient has had a myocardial infarction in the previous 12 weeks. (Prior to study entry, ECG abnormalities at screening must be documented by the investigator as not medically relevant.) l. The patient participated in another clinical investigation within 30 days of enrollment or is receiving another investigational agent.	b. The patient has had a myocardial infarction in the previous 12 weeks. (~~Prior to study entry, ECG abnormalities at screening must be documented by the investigator as not medically relevant.~~ ***Prior to study entry, any other electrocardiogram [ECG] abnormalities noted at screening other than myocardial infarction within the previous 12 weeks and felt by the investigator not to be medically relevant, must be documented as such.***) l. The patient participated in another clinical investigation within 30 days of enrollment or is receiving another investigational agent***, unless discussed with the sponsor***.	the protocol. Clarification.
Chapter/section concerned: 5.1 Study Drugs Administered For both phases (with the exception of cycle 1 of Phase 1 only), patients will receive induction cycles of 14 days twice daily treatment followed by 14 days without treatment (1 induction cycle) for as long as they adequately recover their blood counts and/or until they achieve hematologic response. Patients will then receive maintenance cycles of 7 days twice daily treatment followed by 21 days without treatment (1 maintenance cycle) for as long as they continue to benefit up to a period of 12 months following the first dose. Dose modifications for toxicity are allowed (see Section 5.1.2). If patients are continuing to receive benefit after 12 months, discussion with the sponsor must take place before continuing study agent administration or being given omacetaxine commercially available where omacetaxine is approved. Doses should be administered at 12 hour (±2 hour) intervals. For cycle 1 of Phase 1 only, patients will receive only 1 dose of omacetaxine on day 1, no doses on days 2 and 3, and 2 doses on days 14 through 17 due to the pharmacokinetic objectives of the study (see Table 3).	Chapter/section concerned: 5.1 Study Drugs Administered For both phases (with the exception of cycle 1 of Phase 1 only), patients will receive induction cycles of 14 days twice daily treatment followed by 14 days without treatment (1 induction cycle) for as long as they adequately recover their blood counts and/or until they achieve hematologic response. Patients will then receive maintenance cycles of 7 days twice daily treatment followed by 21 days without treatment (1 maintenance cycle) for as long as they continue to benefit up to a period of 12 months following the first dose. Dose modifications for toxicity are allowed (see Section 5.1.2). If patients are continuing to receive benefit after 12 months, discussion with the sponsor must take place before continuing study agent administration or being given omacetaxine commercially available where omacetaxine is approved. Doses should be administered at 12 hour (±2 hour) intervals. ***Patients who miss 1 day of dosing can make up that missed day as long as there is no more than 1 day interruption in dosing. That dose can added at the end of that cycle as long as it is continuous.*** For cycle 1 of Phase 1 only, patients will receive only 1 dose of omacetaxine on day 1, no doses on days 2 and 3, and 2 doses on days ~~14~~ ***4*** through 17 due to the pharmacokinetic objectives of the study (see Table 3). **Therefore, e**~~**E**~~***ach patient will be scheduled to receive 29 doses during cycle 1.***	Clarification and Typographical clarification of day 14. Correction from Protocol Amendment Letter 10 June 2014.
Chapter/section concerned: 5.1.2. Dose Modifications for Toxicity	Chapter/section concerned: 5.1.2. Dose Modifications for Toxicity	All chemistry and hematology tests have a ±2 day window.

Initial wording	Amended or new wording	Reason/Justification for change
5.1.2.1. Hematologic Toxicity Omacetaxine treatment cycles may be delayed and/or the number of days of dosing during the cycle reduced for hematologic toxicities (eg, neutropenia, thrombocytopenia). Complete blood counts should be performed weekly during the first 5 cycles. After the initial 5 cycles, CBCs should be performed every 2 weeks or as clinically indicated via unscheduled but collected data visits. If a patient experiences grade 4 neutropenia (absolute neutrophil count [ANC] less than $0.5x10^9$/L) or grade 3 thrombocytopenia (platelet counts less than $50x10^9$/L) during a cycle, delay starting the next cycle until ANC is greater than or equal to $1.0x10^9$/L and platelet count is greater than or equal to $50x10^9$/L. Also, for the next cycle, reduce the number of dosing days by 2 days (eg, to 12 or 5 days).	5.1.2.1. Hematologic Toxicity Omacetaxine treatment cycles may be delayed and/or the number of days of dosing during the cycle reduced for hematologic toxicities (eg, neutropenia, thrombocytopenia). Complete blood counts should be performed weekly during the first 5 cycles. After the initial 5 cycles, CBCs should be performed every 2 weeks ***(±2 days)*** or as clinically indicated via unscheduled but collected data visits. If a patient experiences grade 4 neutropenia (absolute neutrophil count [ANC] less than $0.5x10^9$/L) or grade 3 thrombocytopenia (platelet counts less than $50x10^9$/L) during a cycle, delay starting the next cycle until ANC is greater than or equal to $1.0x10^9$/L and platelet count is greater than or equal to $50x10^9$/L. ~~Also, for the next cycle, reduce the number of dosing days by 2 days (eg, to 12 or 5 days).~~ **If the patient should experience a delay as just described, in the next cycle, the number of dosing days can be reduced by 2 days. For example, during induction this would be from 14 days to 12 days; during maintenance, this would be from 7 days to 5 days. If subjects tolerate a cycle with a 2-day reduction without any problems, then the following cycle, the full cycle can be provided. If more than 2 delays occur secondary to grade 4 neutropenia or grade 3 thrombocytopenia with yet another reduction in 2 more days in either induction or maintenance, consideration of discontinuing study medication should be discussed by the treating physician, the designated CRO physician, and the designated Sponsor physician.**	Added for clarification.
Chapter/section concerned: 5.5 Total Blood Volume The total blood volume to be withdrawn for any given patient is difficult to accurately predict and will depend, among other things, on how long the patient receives study drug, whether there are any adverse events leading to unscheduled blood draws, and whether there is any hospitalization related to said adverse events. Therefore, the timing and quantity obtained are defined in general terms as follows: Full serum chemistry laboratory tests are scheduled to be performed at screening, every 2 weeks after cycle 5, and at the end-of-treatment visit. At each time point, 6	Chapter/section concerned: 5.5 Total Blood Volume The total blood volume to be withdrawn for any given patient is difficult to accurately predict and will depend, among other things, on how long the patient receives study drug, whether there are any adverse events leading to unscheduled blood draws, and whether there is any hospitalization related to said adverse events. Therefore, the timing and quantity obtained are defined in general terms as follows: Full serum chemistry laboratory tests are scheduled to be performed at screening, every 2 weeks ***(±2 days)*** after cycle 5, and at the end-of-treatment visit. At each time point, 6 to 7 mL of blood will be drawn.	All chemistry and hematology tests have a ±2 day window. Clarification of every 3 months.

Initial wording	Amended or new wording	Reason/Justification for change
to 7 mL of blood will be drawn. Serum chemistry 7 laboratory tests are scheduled to be performed on day 1 of each cycle, and days 7, 14, and 21 of cycles 1 through 5. At each time point, 6 to 7 mL of blood will be drawn. Hematology laboratory tests are scheduled to be performed at screening, day 1 of each cycle, days 7, 14, and 21 of cycles 1 through 5, day 14 for cycles after cycle 5, at confirmation of response, and at the end-of-treatment visit. At each time point, 4 to 5 mL of blood will be drawn. BCR-ABL transcript levels are scheduled to be performed at screening, every 3 months during the study, at confirmation of response, and at the end-of-treatment visit. At each time point, 3 mL of blood will be drawn. BCR-ABL mutation analysis is to be performed at screening and every 3 months on study. At each time point 3mL of blood will be drawn.	Serum chemistry 7 laboratory tests are scheduled to be performed on day 1 of each cycle, and days 7 ***(±2 days)***, 14 ***(±2 days)***, and 21 ***(±2 days)*** of cycles 1 through 5. At each time point, 6 to 7 mL of blood will be drawn. Hematology laboratory tests are scheduled to be performed at screening, day 1 of each cycle, days 7 ***(±2 days)***, 14 ***(±2 days)***, and 21 ***(±2 days)*** of cycles 1 through 5, day 14 ***(±2 days)*** for cycles after cycle 5, at confirmation of response, and at the end-of-treatment visit. At each time point, 4 to 5 mL of blood will be drawn. BCR-ABL transcript levels are scheduled to be performed at screening, every 3 months ***(ie, every 3 cycles)*** during the study, at confirmation of response, and at the end-of-treatment visit. At each time point, 3 mL of blood will be drawn. BCR-ABL mutation analysis is to be performed at screening and every 3 months ***(ie, every 3 cycles)*** on study. At each time point 3mL of blood will be drawn.	
Chapter/section concerned: 6.2.4 Molecular Response Molecular response is defined by the decrease in the amount of BCR-ABL mRNA measured by reverse transcriptase polymerase chain reaction (RT-PCR) or by the actual percentage of BCR-ABL mNRA transcripts (ratio of BCR-ABL transcript numbers to the number of control gene transcripts) (Baccarani et al 2013, Cross et al 2012, Hughes et al 2006) (see Appendix A).	Chapter/section concerned: 6.2.4 Molecular Response Molecular response is defined by the decrease in the amount of BCR-ABL mRNA measured by reverse transcriptase polymerase chain reaction (RT-PCR) or by the actual percentage of BCR-ABL m~~N~~R**N**A transcripts (ratio of BCR-ABL transcript numbers to the number of control gene transcripts) (Baccarani et al 2013, Cross et al 2012, Hughes et al 2006) (see Appendix A).	Typo corrected to mRNA.
Chapter/section concerned: 7.1.4 Relationship of an Adverse Event to the Study Drug No reasonable possibility (not related) Definition This category applies to adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events, which, after careful medical consideration at the time	Chapter/section concerned: 7.1.4 Relationship of an Adverse Event to the Study Drug No reasonable possibility (not related) Definition This category applies to adverse events ~~which~~ ***that***, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events~~, which~~ ***that***, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	Updated relationship table based on new protocol template language for relationship of an adverse event to study drug categories.

Initial wording	Amended or new wording	Reason/Justification for change
they are evaluated, are judged to be unrelated to the study drug Clarification The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the test drug. • It does not reappear or worsen when the drug is re-administered..	Clarification The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the ~~test~~ ***study*** drug. • It could readily have been produced by the patient's clinical state, environmental**,** or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the ~~test~~ ***study*** drug. • It does not reappear or worsen when the drug is re-administered.	
Chapter/section concerned: 7.1.4 Relationship of an Adverse Event to the Study Drug Reasonable possibility (related) Definition This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty. Clarification The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the drug. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.	Chapter/section concerned: 7.1.4 Relationship of an Adverse Event to the Study Drug Reasonable possibility (related) Definition This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the ~~test~~ ***study*** drug administration cannot be ruled out with certainty. Clarification The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the ***study*** drug. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental**,** or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does	Updated relationship table based on new protocol template language for relationship of an adverse event to study drug categories.

Initial wording	Amended or new wording	Reason/Justification for change
• It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • It follows a known pattern of response to the test drug.	not disappear upon discontinuation of the drug, yet ***a*** drug~~-relatedness~~ ***relationship*** clearly exists. • It follows a known pattern of response to the ~~test~~ ***study*** drug.	
Chapter/section concerned: 7.1.5.3. Reporting a Serious Adverse Event 7.1.5.3.1 Investigator Responsibility To satisfy regulatory requirements, all serious adverse events (as described in Section 7.1.5.1) that occur during or after the study period (including the protocol defined follow up period, described in Section 7.1.2), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it or, if the event occurs on a weekend or national holiday, on the next working day. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them. The serious adverse event form should be sent to the local safety officer (LSO) or other designated personnel (a contract research organization [CRO] in a country without a Sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's Global Patient Safety & Pharmacovigilance Department.. The following information should be provided to record the event accurately and completely: • study number C41443/2057	Chapter/section concerned: 7.1.5.3. Reporting a Serious Adverse Event 7.1.5.3.1 Investigator Responsibility To satisfy regulatory requirements, all serious adverse events (as described in Section 7.1.5.1) that occur during ~~or after~~ the study period (including the protocol**-**defined follow**-**up period, described in Section 7.1.2), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. ~~or, if the event occurs on a weekend or national holiday, on the next working day.~~ Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them. The serious adverse event form should be sent to the local safety officer (LSO) or other designated personnel (a contract research organization [CRO] in a country without a Sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's Global Patient Safety & Pharmacovigilance Department.. The following information should be provided to record the event accurately and completely: • study number C41443/2057 • investigator and investigational center identification • patient number • patient initials	Revised specifics for reporting serious adverse events section based on new protocol template.

Initial wording	Amended or new wording	Reason/Justification for change
• investigator and investigational center identification • patient number • patient initials • onset date and description of adverse event • investigator's assessment of the relationship of the adverse event to the study drug (no reasonable possibility, reasonable possibility) Additional information may include the following: • age and sex of patient • date of first dose of study drug • date and amount of last administered dose of study drug • action taken • outcome, if known • severity • concomitant therapy (including doses, routes, and regimens) and treatment of the event • pertinent laboratory or other diagnostic test data • medical history • results of dechallenge/rechallenge, if known • for an adverse event resulting in death: – cause of death (whether or not the death was related to study drug) – autopsy findings (if available) In the US, the investigator must ensure that the IRB is also informed of the event, in accordance with local regulations. In the EU, the sponsor or its designee must ensure that the IEC is also informed of the event, in accordance with local regulations.	• onset date and description of adverse event • investigator's assessment of the relationship of the adverse event to the study drug (no reasonable possibility, reasonable possibility) Additional information may include the following: • age and sex of patient • date of first dose of study drug • date and amount of last administered dose of study drug • action taken • outcome, if known • severity • ***explanation of assessment of relatedness*** • concomitant therapy (including doses, routes, and regimens) and treatment of the event • pertinent laboratory or other diagnostic test data • medical history • results of dechallenge/rechallenge, if known • for an adverse event resulting in death: – cause of death (whether or not the death was related to study drug) – autopsy findings (if available) ~~In the US, the investigator must ensure that the IRB is also informed of the event, in accordance with local regulations. In the EU, the sponsor or its designee must ensure that the IEC is also informed of the event, in accordance with local regulations.~~ Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease. ~~On the basis of this assessment, a decision will be made concerning the need for further medical intervention.~~ Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigational center within 24 hours of when it becomes known to the same address as the initial report.	

Initial wording	Amended or new wording	Reason/Justification for change
Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease. On the basis of this assessment, a decision will be made concerning the need for further medical intervention. Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigational center within 24 hours of when it becomes known to the same address as the initial report. For all countries, the sponsor's Global Patient Safety & Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for local submission to the regulatory authorities and IEC/IRBs and Investigators, according to regulations. Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.2).	For all countries, the sponsor's Global Patient Safety & Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/***extensible markup language (***XML***)*** file to the LSO/CRO for local submission to the regulatory authorities and IEC/IRBs and Investigators, according to regulations. ***The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with local regulations.*** Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.2).	
Chapter/section concerned: 7.1.5.3. Reporting a Serious Adverse Event 7.1.5.3.2 Sponsor Responsibility If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all Investigators participating in sponsored clinical studies of omacetaxine and the appropriate regulatory authorities. In addition to notifying the investigators and regulatory authorities, other measures may be required, including the following:	Chapter/section concerned: 7.1.5.3. Reporting a Serious Adverse Event 7.1.5.3.2 Sponsor Responsibility If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all Investigators participating in sponsored clinical studies of omacetaxine and the appropriate regulatory authorities ***(and IEC/IRB, if appropriate).*** In addition to notifying the investigators and regulatory authorities ***(and IEC/IRB, if appropriate)***, other measures may be required, including the following:	Revised specifics for reporting serious adverse events section based on new protocol template.
Chapter/section concerned: 7.3 Clinical Laboratory Tests Clinical laboratory tests (serum chemistry and hematology) will be performed at screening, prior to each treatment cycle, every 7 days during the first 5	Chapter/section concerned: 7.3 Clinical Laboratory Tests Clinical laboratory tests (serum chemistry and hematology) will be performed at screening, prior to each treatment cycle, every 7 days ***(±2 days)*** during the first 5 cycles, and every 2 weeks	All chemistry and hematology tests have a ±2 day window.

Initial wording	Amended or new wording	Reason/Justification for change
cycles, and every 2 weeks during later cycles, as clinically indicated, and at the end-of-treatment visit.	***(±2 days)*** during later cycles, as clinically indicated, and at the end-of-treatment visit.	
Chapter/section concerned: 7.5 Electrocardiography A 12 lead ECG will be conducted at screening, prior to dosing on day 1 of cycles 1 through 3, optionally after completion of treatment on day 14 of cycle 1, every 3 months during the study, and at the end-of-treatment visit.	Chapter/section concerned: 7.5 Electrocardiography A 12 lead ECG will be conducted at screening, prior to dosing on day 1 of cycles 1 through 3, optionally after completion of treatment on day 14 of cycle 1, every 3 months ***(ie, every 3 cycles)*** during the study, and at the end-of-treatment visit. ***Prior to study entry, any other ECG abnormalities noted at screening other than myocardial infarction within the previous 12 weeks and felt by the investigator not to be medically relevant, must be documented as such.***	Clarification of every 3 months. Text added for clarification and consistency between protocol sections.
Chapter/section concerned: Appendix A. RESPONSE EVALUATION CRITERIA 1.Hematologic Response A. Complete Hematologic Response (CHR) • CP CML: – WBC<10 x 109/liter – platelets <450 x 109/liter – myelocytes + metamyelocytes <5% in blood – no blasts or promyelocytes in peripheral blood – <20% basophils in peripheral blood – no extramedullary involvement – response must last at least 8 weeks • AP CML: – ANC ≥1.5 x 109/liter – platelets ≥100 x 109/liter – no blood blasts – bone marrow blasts <5% – no extramedullary disease – response must last at least 4 weeks • Loss of CHR in CP CML: – WBC >20 x 109/liter – loss of any of the other response criteria or progression to accelerated	Chapter/section concerned: Appendix A. RESPONSE EVALUATION CRITERIA 1.Hematologic Response A. Complete Hematologic Response (CHR) • CP CML: – WBC<10 x 10^9/liter – platelets <450 x 10^9/liter – myelocytes + metamyelocytes <5% in blood – no blasts or promyelocytes in peripheral blood – <20% basophils in peripheral blood – no extramedullary involvement – response must last at least 8 weeks • AP CML: – ANC ≥1.5 x 10^9/liter – platelets ≥100 x 10^9/liter – no blood blasts – bone marrow blasts <5% – no extramedullary disease – response must last at least 4 weeks • Loss of CHR in CP CML: – WBC >20 x 10^9/liter – loss of any of the other response criteria or progression to accelerated phase or blast crisis or discontinuation due to progressive disease or death	Typographical correction. Font changed to superscript.

Initial wording	Amended or new wording	Reason/Justification for change
phase or blast crisis or discontinuation due to progressive disease or death		
Chapter/section concerned: Appendix A. RESPONSE EVALUATION CRITERIA 1.Hematologic Response B. Parial Hematologic Response (PHR) Same criteria as for CHR but with 1 or more of the following being present: • persistence of splenomegaly (although with a reduction of ≥50% from pretreatment size) • platelets >450 x 109/liter	Chapter/section concerned: Appendix A. RESPONSE EVALUATION CRITERIA 1.Hematologic Response B. Parial Hematologic Response (PHR) Same criteria as for CHR but with 1 or more of the following being present: • persistence of splenomegaly (although with a reduction of ≥50% from pretreatment size) • platelets >450 x 10^9/liter	Typographical correction. Font changed to superscript.
Chapter/section concerned: Appendix A. RESPONSE EVALUATION CRITERIA 1.Hematologic Response C. Hematologic Improvement (HI) Same criteria as CHR except for allowing thrombocytopenia lower than 100 x 109/L caused by underlying disease and the presence of a few immature cells (no blasts or promyelocytes, 5% or fewer myelocytes plus metamyelocytes) in the peripheral blood.	Chapter/section concerned: Appendix A. RESPONSE EVALUATION CRITERIA 1.Hematologic Response C. Hematologic Improvement (HI) Same criteria as CHR except for allowing thrombocytopenia lower than 100 x 10^9/L caused by underlying disease and the presence of a few immature cells (no blasts or promyelocytes, 5% or fewer myelocytes plus metamyelocytes) in the peripheral blood.	Typographical correction. Font changed to superscript.
Chapter/section concerned: Appendix D. LABORATORY TESTS Serum Chemistry • Full Serum Chemistry – uric acid, ALT, AST, total bilirubin, blood glucose, BUN or urea, potassium, sodium, chloride, CO2 content (ie bicarbonate), creatinine, alkaline phosphatase, phosphorus, other	Chapter/section concerned: Appendix D. LABORATORY TESTS Serum Chemistry • Full Serum Chemistry – uric acid, ALT, AST, total bilirubin, blood glucose, BUN or urea, potassium, sodium, chloride, CO_2 content (ie bicarbonate), creatinine, alkaline phosphatase, phosphorus, other	Typographical correction. Font changed to subscript.

17.2. Administrative Letter Dated 10 June 2014

Global Branded Products

To: [redacted]

From: Teva Branded Pharmaceutical Products R&D, Inc.

Date: June 10, 2014

RE: SRC Clarification #1

Study #: PH 254914

Study Title: (C41443/2057) An Open-Label, Single-Group Clinical Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Omacetaxine Mepesuccinate Given Subcutaneously as a Fixed Dose in Patients with Chronic Phase or Accelerated Phase Chronic Myeloid Leukemia who have Failed 2 or More Tyrosine Kinase Inhibitor Therapies (referred to as the **SYNSINCT** study) Original Dated 04Dec2013; Listed in http://clinicaltrials.gov/ct2/show/NCT02078960?term=omacetaxine+2057&rank=1

The following change has been made to the aforementioned protocol as part of a clarification to expedite the review process:

Explanation of Typographical Clarification

Sections of the protocol - page 58, Section 5. TREATMENT OF PATIENTS, 5.1. Study Drugs Administered, fourth paragraph:

Current text - For cycle 1 of Phase 1 only, patients will receive only 1 dose of omacetaxine on day 1, no doses on days 2 and 3, and 2 doses on days 14 through 17 due to the pharmacokinetic objectives of the study (see Table 3).

Clarified text – For cycle 1 of Phase 1 only, patients will receive only 1 dose of omacetaxine on day 1, no doses on days 2 and 3, and 2 doses on days 4 through 17 due to the pharmacokinetic objectives of the study (see Table 3).

This typographical protocol clarification will not affect the informed consent form. This information is correct in other parts of the protocol including Table 3 in the protocol, the diary card, and in the eCRF (case report forms). Please file a copy of this letter with the protocol for reference until a future protocol amendment will be provided.

Teva Pharmaceuticals
41 Moores Road, PO Box 4011 | Frazer, PA 19355 | [redacted] | www.tevapharm.com

If you have any questions please do not hesitate to contact me at the below information.

Sincerely,

APPENDIX A. RESPONSE EVALUATION CRITERIA

1. Hematologic Response

A. Complete Hematologic Response (CHR)

- CP CML:
  - WBC<10 x 10^9/liter
  - platelets <450 x 10^9/liter
  - myelocytes + metamyelocytes <5% in blood
  - no blasts or promyelocytes in peripheral blood
  - <20% basophils in peripheral blood
  - no extramedullary involvement
  - response must last at least 8 weeks
- AP CML:
  - ANC ≥1.5 x 10^9/liter
  - platelets ≥100 x 10^9/liter
  - no blood blasts
  - bone marrow blasts <5%
  - no extramedullary disease
  - response must last at least 4 weeks
- Loss of CHR in CP CML:
  - WBC >20 x 10^9/liter
  - loss of any of the other response criteria or progression to accelerated phase or blast crisis or discontinuation due to progressive disease or death

In patients who receive hydroxyurea during the first 2 cycles of treatment, if clinically indicated to control disease, CHR must be sustained for ≥4 weeks for AP CML and for ≥8 weeks for CP CML following the discontinuation of hydroxyurea to be considered a CHR.

Treatment-related suppression of peripheral blood counts (PBC) due to continuing maintenance courses of omacetaxine therapy will not impact on the requirement for normal peripheral blood counts and ANC in calculation of the duration of CHR if it is clear that PBC suppression is temporarily due to the prior omacetaxine maintenance treatment course, eg, occurring at the expected time for nadir blood counts following a treatment cycle of omacetaxine, and the PBC suppression is transient.

B. Partial Hematologic Response (PHR)

Same criteria as for CHR but with 1 or more of the following being present:

- persistence of splenomegaly (although with a reduction of ≥50% from pretreatment size)
- platelets >450 x 10^9/liter
- presence of immature cells in peripheral blood (no blasts or promyelocytes, 5% or fewer myelocytes plus metamyelocytes)
- 5% to 25% blasts in the bone marrow
- in patients with EMD pretreatment, there must be a reduction by ≥50% of EMD

C. Hematologic Improvement (HI)

Same criteria as CHR except for allowing thrombocytopenia lower than 100 x 10^9/L caused by underlying disease and the presence of a few immature cells (no blasts or promyelocytes, 5% or fewer myelocytes plus metamyelocytes) in the peripheral blood. Patients meeting the CHR with thrombocytopenia cased by omacetaxine therapy will be considered to have achieved a CHR.

D. Return to Chronic Phase (RCP) for patients in AP CML

- <15% blasts bone marrow and peripheral blood
- <30% blasts + promyelocytes in the bone marrow and peripheral blood
- <20% basophils in peripheral blood
- no extramedullary disease other than spleen and liver

2. Cytogenetic Response

- Complete: No Ph-positive metaphases
- Partial: 1 to 35% Ph-positive metaphases
- Major: 0 to 35% Ph-positive metaphases (complete and partial)

- Minor: >35% Ph-positive metaphases
- Minimal: >65% to 95% Ph+ cells
- None: >95%Ph+ cells
- Not Done: <20 metaphases were examined and/or response could not be assigned

A minimum of 20 metaphases should be examined.

Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation; thus, unconfirmed CCyR or partial cytogenetic response (PCyR) might have a lesser cytogenetic response on a subsequent bone marrow evaluation. A confirmed cytogenetic response is based on 2 bone marrow cytogenetic evaluations, the latter done at least 1 month after the initial bone marrow study.

Cytogenetic response evaluation will be based on standard cytogenetic analysis (at least 20 metaphases). This condition will always be required for affirmation or complete cytogenetic response. However, an assessment of partial response will remain in a sample with <20 metaphases when it is immediately preceded or followed by a complete or partial cytogenetic response in another sample.

3. No evidence of leukemia (NEL)-CML AP

Morphologic leukemia free state, defined as <5% bone marrow blasts

4. Molecular Response

Molecular response is best assessed according to the International Scale (IS) as the ratio of BCR-ABL1 transcripts to ABL1 transcripts, or other internationally recognized control transcripts. It is expressed and reported as BCR-ABL1% on a log scale, where 10%, 1%, 0.1%, 0.01%, 0.0032%, and 0.001% correspond to a decrease of 1, 2, 3, 4, 4.5, and 5 logs, respectively, below the standard baseline that was used in the International Randomized Study if Interferon Versus ST1571 (IRIS) study (Baccarani et al 2013, Cross et al 2012, Hughes et al 2006).

- Major Molecular Response: a BCR-ABL1 expression of ≤0.1%
- Other definitions for deep molecular responses and undetectable disease are as described in Baccarani et al (2013).

APPENDIX B. MOLECULAR STUDIES

BCR ABL Transcripts Levels and BCR-ABL Mutation Analysis

1. The analysis may be done locally.

2. Type of BCR-ABL transcripts, BCR-ABL transcript levels by quantitative reverse transcription PCR (qRT-PCR) and, as indicated in the protocol, BCR-ABL kinase mutation analysis of peripheral blood samples will be performed.

3. Please check with your investigational center's laboratory for volume requirements and sample handling.

4. If the investigational center is not able to carry this out at the investigational center, the sponsor may assist with arrangements for a central lab to perform these tests. For further advice, please contact the CRO or the back-up global clinical operations representative found on the first pages of the protocol or refer to the Pharmacokinetics and Laboratory Manual.

5. The definition of Molecular Response is found in Appendix A.

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

APPENDIX D. LABORATORY TESTS

Hematology

- White blood cell, red blood cells, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, mean platelet volume, platelet count, neutrophils, ANC, band neutrophils, lymphocytes, monocytes, eosinophils, basophils, metamyelocytes, promyelocytes, myelocytes, blasts, other

Serum Chemistry

- Full Serum Chemistry
  - uric acid, ALT, AST, total bilirubin, blood glucose, BUN or urea, potassium, sodium, chloride, CO_2 content (ie bicarbonate), creatinine, alkaline phosphatase, phosphorus, other
  - direct bilirubin, only if clinically indicated
- Serum Chemistry 7
  - sodium, chloride, CO_2 content, creatinine, BUN or urea, blood glucose, and potassium only

Special tests

- Bone marrow aspiration (or biopsy) and cytogenetics

Urinalysis

- specific gravity, pH, glucose, protein, blood, bilirubin, ketones, urobilinogen, nitrite, leukocytes, color, appearance, other