Statistical Analysis Plan

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

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TEVA BRANDED PHARMACEUTICAL PRODUCTS R&D, INC.

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Study C41443/2057 **Phase** 1/2

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AP	Accelerated phase
AUC	area under the plasma drug concentration by time curve
$AUC_{0-\infty}$	area under the plasma drug concentration by time curve from 0 to infinite time
AUC_{0-t}	area under the plasma drug concentration by time curve from 0 to time of the last measurable plasma concentration
AUC_{0-12}	area under the plasma drug concentration by time curve from time 0 to the 12-hour time point
BSA	Body Surface Area
CI	Confidence interval
CL/F	apparent plasma clearance
CRF	Case report forms
C_{max}	maximum observed plasma concentration
CML	Chronic myeloid leukemia
CP	Chronic phase
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ICH	International Conference on Harmonization
MaHR	Major hematology response
MCyR	Major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression-free survival
Ph+	Philadelphia chromosome-positive
PK	Pharmacokinetic
PP	Per protocol
R_{pred}	predicted accumulation ratio
SAP	Statistical Analysis Plan

SD	Standard Deviation
SE	Standard Error
$t_{1/2}$	apparent terminal elimination half-life
t_{max}	time to maximum observed plasma drug concentration
TKI	Tyrosine kinase inhibitor
V_z/F	apparent volume of distribution
WBC	White blood cell
WHO	World Health Organization
λ_z	apparent plasma terminal elimination rate constant

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for TEVA Branded Pharmaceuticals Products R&D, Inc. study 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 (CP) or Accelerated Phase (AP) Chronic Myeloid Leukemia (CML) who have Failed 2 or More Tyrosine Kinase Inhibitor Therapies), and was written in accordance with SOP-0000930 (Global Statistical Analysis Plan Preparation, Review and Approval).

This phase 1/2 study is being completed to assess the safety and efficacy of omacetaxine mepesuccinate given subcutaneously as a fixed dose in patients with CP or AP CML who have failed 2 or more tyrosine kinase inhibitor therapies.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association, and the Royal Statistical Society, for statistical practice.

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study. When differences exist in descriptions or explanations provided in the protocol and this SAP, the SAP prevails; the discrepancies will be explained in the CSR.

Since the study was prematurely terminated during the phase 1 part of the study due to poor recruitment, this SAP is adpated to support the abbreviated clinical study report.

1. STUDY OBJECTIVES

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 Tyrosine kinase inhibitor (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.

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
- to characterize the pharmacokinetic profile of omacetaxine in cycle 1 when administered subcutaneously as a fixed dose

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

2. STUDY DESIGN

2.1. 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 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 body surface area (BSA) 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 protocol 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; the number of consecutive doses of omacetaxine or intervals between subsequent cycles may be adjusted, as clinically indicated, according to guidelines provided in protocol Section 5.1.2.

See more details in the protocol.

Visit-specific procedures and assessments are outlined in Table 1.

Table 1: Study Procedures and Assessments

Procedures and assessments	Screening[a]	Omacetaxine induction or maintenance treatment 28-day cycles (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[d] on study	Confirmation of response		
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[r,v]			
Urinalysis	X								
Document other measures of	X	X	X					X	

Procedures and assessments	Screening[a]	Omacetaxine induction or maintenance treatment 28-day cycles (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[d] on study	Confirmation of response[e]		
disease and disease symptoms									
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.

[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.

[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 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, temperature) within 30 minutes prior to administration of omacetaxine and 20 minutes after administration 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] May be omitted if prior study available within preceding 30 days.
[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.
[l] Electrocardiogram after completion of day 14 of treatment, induction cycle 1, if the patient is available for this exam.
[m] Complete blood counts 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 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, 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).
[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.
[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.

2.2. Primary and Secondary Measures and Endpoints

2.2.1. 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 protocol Appendix A for the measures for response.

2.2.2. 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 in patients with AP CML, as defined above, to the earliest date of objective evidence of disease progression (ie, development of AP-phase CML in patients with CP CML or disease progression as recorded on eCRF for patients with AP CML), relapse (ie, loss of complete hematologic response in patient with AP CML or major cytogenetic response), death, or treatment discontinuation due to toxicity or lack of efficacy
- molecular response by site (peripheral transcript of BCR-ABL) (see protocol Appendix A) assessed every 3 months
- 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-phase CML in patients with CP CML or disease progression as recorded on eCRF for patients with AP CML), relapse (ie, loss of complete hematologic response in patient with AP CML or major cytogenetic response), death, or treatment discontinuation due to toxicity or lack of efficacy
- overall survival, defined as the time interval from date of first dose to date of death from any cause

2.2.3. 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 electrocardiogram (ECG)
- concomitant medication usage

2.2.4. Pharmacokinetic Measures and Endpoints

The following pharmacokinetic parameters for omacetaxine and its metabolites, 4'-DMHHT and cephalotaxine, 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; omacetaxine only)
- apparent volume of distribution (V_z/F; omacetaxine only)
- predicted accumulation ratio (R_{pred}) calculated as $AUC_{0-\infty}/AUC_{0-12}$

2.3. 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.

2.4. Randomization and Blinding

This is a nonrandomized, open-label study.

2.5. Sequence of Planned Analyses

2.5.1. Interim Analyses

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.

The analyses identified in Section 10.1 will be performed.

2.5.2. Final Analyses and Reporting

All final, planned analyses identified in this SAP will be performed only after the last patient has completed the study.

Any exploratory analyses completed to support study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR.

3. POPULATIONS /ANALYSIS SETS

3.1. Enrolled Patients

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.

3.2. Safety Analysis Set

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

3.3. Per-Protocol Analysis Set

Due to study early termination with a very limited number of patients, per-protocol (PP) analysis set will be defined but no analyses will be performed on PP analysis set.

3.4. Pharmacokinetic Analysis Set

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

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include n, mean, standard deviation, standard error of the mean, median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages.

Summaries of clinically significant abnormal values will include all postbaseline values (including scheduled, unscheduled, and early termination visits).

Endpoint for analyses and summaries is the last observed postbaseline data.

4.2. Specification of Baseline Values

Baseline is the last observed data prior to the first dose of study drug.

4.3. Multiple Comparisons and Multiplicity

There are no multiple comparisons or multiplicity in this study.

4.4. Handling Withdrawals and Missing Data

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.

4.4.1. Partial Dates

Dates that have incomplete information, such as only the month and year or just the year, will be estimated for the purpose of calculating variables that are dependent on time if necessary.

For partial dates of CML diagnosis, day will be estimated as the first day (01) of the month (if month and year of partial date are available) or middle (July 1) of the year (if only year is available).

The imputations for partial dates are only for calculation purpose. Original date variables will not be imputed. Listings will list partial dates.

4.5. Study Days and Visit Windows

For by-visit summaries, if there are multiple assessments at a postbaseline visit then the last non-missing assessment at that visit will be used for the summary. This includes assessments at the scheduled and unscheduled visits.

Study days will be numbered relative to the first day of study drug administration. The start of treatment (day 1) is defined as the date on which a patient takes the first dose of study drug, as recorded on the study drug diary. Days will be numbered relative to study start (ie, ..., –2, –1, 1, 2, ...; with day 1 being the start of study drug and day –1 being the day before the start of study drug).

5. STUDY POPULATION

5.1. General

The set of enrolled patients will be used for all study population summaries unless otherwise noted.

For safety and efficacy analysis, summaries will be presented by BSA cohort and overall.

5.2. Patient Disposition

Patients screened, patients screened but not enrolled and the reason will be summarized for the overall group using patient counts.

Patients enrolled, patients enrolled but not treated, patients in the safety, PP, and PK analysis sets, number of cycle treated, patients who completed study treatment, patients who did not complete the treatment and reason, patients who completed the study, and patients who withdrew from the study and reason will be summarized using descriptive statistics.

The denominator for calculating the percentages will be the number of enrolled patients.

5.3. Demographics and Baseline Characteristics

Demographics at baseline will be examined. The continuous variables of patient age, weight, height, and BSA will be summarized using descriptive statistics. The categorical variables of age group (<65 years, >=65 years), patient sex, race, and ethnicity will be summarized using descriptive statistics for each category.

Data will be presented for the enrolled patients.

Baseline characteristics including New York Heart Assiciation (NYHA) function class, Eastern Cooperative Oncology Group (ECOG) performance status, liver examination, spleen examination, size below left and right costal margin (cm), extramedullary involvement (yes/no), and chest X-ray will be summarized using descriptive statistics.

Category for missing data will be provided as necessary.

5.4. Cancer and Glucose History

Phase of CML at diagnosis, phase of CML at study entry (Chronic Phase vs. Accelerated Phase), glucose intolerance (yes/no), and diabetes mellitus (yes /no) will be summarized using descriptive statistics.

If applicable, age at onset of the first CML diagnosis and months since diagnosis of the first CML diagnosis to the first dose of study drug will be calculated and summarized using descriptive statistics.

Age at onset of first CML diagnosis= (date of first CML diagnosis – date of birth +1)/365.25, rounded to one decimal place.

Months since diagnosis to the first dose of study drug = (date of first administration of study drug – date of first CML diagnosis +1)/30.44, rounded to one decimal place.

5.5. Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 16.1). Patients with a medical history assessment, patients with at least 1 abnormal finding, and abnormal findings for each system organ class (SOC) will be summarized using descriptive statistics.

5.6. Prior Leukemia Treatment

Prior leukemia treatment will be coded using the World Health Organization dictionary of medical codes (WHO Drug version March 2013). The incidence of prior leukemia treatment will be summarized using descriptive statistics by therapeutic class and preferred term.

Best hematologic response, best cytogenetic response, and best molecular response will be summarized using descriptive statistics.

5.7. Prior Medications

All prior medications will be coded using WHO Drug (version March 2013). The incidence of prior medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior medications will include all medications taken prior to the first day of study drug treatment.

Usage of prior hydroxyurea, anagrelide, and leukapheresis will be summarized separately.

5.8. Electrocardiography

Electrocardiogram findings (normal, abnormal and clinically significant, and abnormal not clinically significant) at baseline will be summarized using descriptive statistics.

5.9. Physical Examinations

Physical examinations abnormality findings at baseline will be summarized using descriptive statistics.

5.10. Protocol Violations

Patients with at least 1 protocol violation for each category will be summarized using descriptive statistics.

6. EFFICACY ANALYSIS

6.1. General

Efficacy analyses will be based on the safety analysis set unless otherwise noted. Efficacy analyses will only include the evaluation of response (cytogenetic and hematologic responses by adjudication or assessed by study sites).

Due to study early termination in Phase 1 portion, efficacy analyses will be performed for Phase 1 portion of the study only.

6.1.1. Sub-group Analysis Variables

No sub-group analyses are performed for efficacy variables due to early termination of the study.

6.2. Primary Efficacy Variable(s) and Analysis

Due to study early termination with very limited number of patients, primary efficacy variable will be derived by adjudication by the Data Monitoring Committee and will be summarized by visit using descriptive statistics.

6.3. Secondary Efficacy Variables and Analyses

Due to study early termination with very limited number of patients, no secondary efficacy variables will be derived and thus no analyses for secondary efficacy variables will be performed.

6.4. Other Analyses

Following post-baseline data will be summarized using descriptive statistics by visit:

- Evaluation of response (cytogenetic and hematologic responses assessed by study sites);
- Liver and spleen examination and extramedullary involvement;
- Bone marrow aspiration and cytogenetic.

7. SAFETY ANALYSIS

7.1. General

The safety analysis set will be used for all safety analyses. Summaries will be presented by BSA cohort and overall unless specified otherwise.

7.2. Study Drug Administration

Duration of treatment, number of days treated (overall and in each cycle), total dose received (mg, overall and in each cycle), and number of cycle treated per patient will be summarized using descriptive statistics. Cycle delay and reason will be summarized by cycle.

Duration of treatment (day) is defined as the time duration from the first dose to the last day of treatment (last day of study drug – first day of study drug + 1).

7.3. Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 16.1). The severity of each adverse event will be graded according to the NCI CTCAE (version 4.0). Summaries will be presented for all adverse events (overall and by NCI CTCAE toxicity grade), adverse events leading to drug withdrawal, adverse events determined by the investigator to be treatment-related (overall and by NCI CTCAE toxicity grade), serious adverse events, adverse events with NCI CTCAE toxicity grade of 3 or higher and non serious adverse events. Adverse events occurring prior to the first day of study drug administration will be considered to be “Non Treatment Emergent” adverse events and those occurring on or after the first day of study drug administration as “Treatment Emergent” adverse events.

The incidence of adverse events will be summarized using descriptive statistics by system organ class and preferred term. Patients are counted only once in each system organ class, and only once in each preferred term category. Treatment-related adverse event summaries will include adverse events with missing relationship to study drug. For the summaries by NCI CTCAE toxicity grade, patients are counted at the greatest severity. Adverse events missing the flag indicating serious will be excluded from the summary of serious adverse events but included in the summary of non serious adverse events.

Listings for fatal adverse events, serious adverse events, adverse events leading to drug withdrawal, adverse events with NCI CTCAE grade of 3 or higher, MedDRA dictionary terms for adverse event descriptions, and adverse event preferred terms by patient number will be presented.

7.4. Deaths

If any patient dies during the study all relevant information will be discussed in the patient’s narratives included in CSR.

7.5. Clinical Laboratory Tests

Clinical laboratory tests (serum chemistry and hematology) will be performed at screening, each cycle in various timepoints, and study completion/early termination.

Selected lab tests will be graded for abnormalities using NCI CTCAE version 4.0. Summary statistics for abnormalities of these selected chemistry and hematology laboratory tests will be presented for overall (worst value in study), by-cycle (worst value in each cycle), at study completion/early termination, and endpoint. For chemistry lab tests with NCI CTCAE grades in two directions (Low and High), data will be presented for both low and high for these tests.

Listings for all laboratory data and for NCI CTCAE grade 3 or 4 laboratory data will be presented.

The criteria for identifying abnormalities are specified in Table 2.

Table 2: NCI CTCAE v4.0 Severity Criteria for Clinical Laboratory Tests

Chemistry	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Albumin (g/l)	<LLN-30	<30 – 20	<20	--
Alk. Phosphatase	>ULN-2.5×ULN	>2.5-5.0×ULN	>5.0-20.0×ULN	>20.0×ULN
AST (SGOT)	>ULN-3.0×ULN	>3.0-5.0×ULN	>5.0-20.0×ULN	>20.0×ULN
ALT (SGPT)	>ULN-3.0×ULN	>3.0-5.0×ULN	>5.0-20.0×ULN	>20.0×ULN
Calcium (mmol/L) Hypercalcemia (High) Hypocalcemia (Low)	 >ULN-2.9 -- <LLN-2.0	 >2.9-3.1 -- <2.0 -1.75	 >3.1-3.4 -- <1.75- 1.5	 >3.4 -- <1.5
Glucose (mmol/L) Hyperglycemia (High) Hypoglycemia (Low)	 >ULN-8.9 -- <LLN-3.0	 >8.9-13.9 -- <3.0 – 2.2	 >13.9-27.8 -- <2.2 - 1.7	 >27.8 -- <1.7
Potassium(mmol/L) Hyperkalemia (High) Hypokalemia (Low)	 >ULN-5.5 -- <LLN-3.0	 >5.5-6.0 -- NA	 >6.0-7.0 -- <3.0 - 2.5	 >7.0 -- <2.5
Sodium(mmol/L) Hypernatremia (High) Hyponatremia (Low)	 >ULN-150 -- <LLN-130	 >150-155 -- NA	 >155-160 -- <130 - 120	 >160 -- <120
Total Bilirubin	>ULN-1.5×ULN	>1.5-3.0×ULN	>3.0-10.0×ULN	>10.0×ULN
Creatinine	>ULN-1.5×ULN	>1.5-3.0×ULN	>3.0-6.0×ULN	>6.0×ULN
Hematology	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin (g/L)	<LLN- 100	<100 – 80	<80 - 65	< 65*
Neutrophils ABS (ANC) ($\times 10^9$/L)	<LLN-1.5	<1.5-1.0	<1.0-0.5	<0.5
Platelet count ($\times 10^9$/L)	<LLN-75.0	<75.0-50.0	<50.0 - 25.0	<25.0
WBC count ($\times 10^9$/L)	<LLN-3.0	<3.0-2.0	<2.0 - 1.0	<1.0
Lymphocytes (ALC) ($\times 10^9$/L)	<LLN-0.8	<0.8 - 0.5	<0.5-0.2	<0.2

ULN=upper limit of normal range; LLN = lower limit of normal; Alk. Phosphatase=Alkaline Phosphatase; AST (SGOT) =Aspartate Aminotransferase; ALT (SGPT) =Alanine Aminotransferase; ANC=absolute neutrophil count; ALC=absolute lymphocyte count; ABS=absolute; WBC=White Blood Cell.

*NCI CTCAE v4.0 does not provide numeric cut-off value for grade 4 hemoglobin. The criterion from NCI CTCAE v3.0 is used.

If Neutrophils and Lymphocytes are collected in unit %, the tests will be converted into the value in the unit $10E^9$/L [absolute (ABS): value in % times WBC/100].

7.6. Vital Signs

Vital signs will be collected at screening, day 1 of each cycle (30 minutes pre dose and 20 minutes post dose) and study completion/early termination.

Vital signs values and changes from baseline to each post-baseline assessment and endpoint will be summarized using descriptive statistics. The incidence of clinically significant abnormal values will be summarized for selected vital signs using descriptive statistics.

Table 3 specifies the criteria for identifying vital signs as clinically significant abnormal. Note that in order to be identified as clinically significant abnormal, a value would need to meet both conditions below: ie, have a value beyond the criterion value and a change of at least the magnitude specified in the change from baseline column.

Table 3: Criteria for Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Pulse	≥120 bpm	Increase of ≥15
	≤50 bpm	Decrease of ≥15
Systolic blood pressure	≥180 mm Hg	Increase of ≥20
	≤90 mm Hg	Decrease of ≥20
Diastolic blood pressure	≥105 mm Hg	Increase of ≥15
	≤50 mm Hg	Decrease of ≥15
Body temperature	≥38.3°C	Change of ≥1.1°C

A listing for clinically significant abnormal vital signs will be presented.

7.7. Electrocardiography

Electrocardiography (ECG) will be collected at screening, day 1 of cycles 1 to 3 and day 14 of cycle 1, every 3 months, and study completion/early termination. Post-baseline assessments will be done pre-dose and post dose except for study completion/early termination assessment.

For ECG findings (normal, abnormal and clinically significant, and abnormal not clinically significant), shifts from baseline to overall, each post-baseline assessment, and endpoint will be summarized using patient counts. For overall, the worst postbaseline finding (the abnormal finding if there are both normal and abnormal findings) for the patient will be summarized.

ECG variables results and changes from baseline to each post-baseline assessment and endpoint will be summarized using descriptive statistics.

7.8. ECOG Performance Status

ECOG performance status will be assessed at screening, on day 1 or within 3 days prior to start of each treatment cycle, and study completion/early termination.

Change from baseline to overall (worst value), each post-baseline assessment, and endpoint will be summarized using descriptive statistics. Changes will be categorized as 'improved', 'staying the same', and 'deteriorated'.

7.9. Physical Examinations

Physical examinations will be performed at screening, on day 1 or within 3 days prior to start of each treatment cycle, and study completion/early termination

Shift from baseline to each post-baseline assessment and endpoint will be summarized using descriptive statistics.

7.10. Concomitant Therapy

All concomitant medications will be coded using the WHO Drug. The incidence of concomitant medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Concomitant medications will include all medications taken while the patient takes study drug.

Usage of hydroxyurea, anagrelide, and leukapheresis will be summarized separately.

8. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

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 metabolite 4'-DMHHT, will be calculated for each patient, when possible, from plasma concentrations obtained following the first dose of omacetaxine in Phase 1. Since all measurements of concentration for cephalotaxine were zero, none of the pharmacokinetic parameters will be calculated and no summaries will be performed for cephalotaxine.

- 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})
- 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; omacetaxine only)
- apparent volume of distribution (V_z/F; omacetaxine only)

8.2. Blood Sampling

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 protocol Section 5.1.

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 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

8.2.2. Phase 2

Due to study early termination in Phase 1, no blood samples were collected for Phase 2.

8.3. Pharmacokinetic Analysis

The pharmacokinetic analysis set will be used for all pharmacokinetic analyses.

The pharmacokinetic parameter data will be summarized by BSA categories and overall using descriptive statistics, including n, mean, standard deviation (SD), standard error (SE), geometric mean (if appropriate), coefficient of variation (if appropriate), median, minimum, and maximum.

The plasma concentration data obtained following the first dose (ie, predose through 72 hr postdose) will similarly be summarized at each nominal time point.

Listings of all available pharmacokinetic parameter and plasma concentration data will be provided.

9. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® version 9.3.

10. LIST OF SUMMARIES AND LISTINGS

10.1. Summary Tables

Summary number	Title	Population
15.1	Patient Disposition (for Phase 1)	All Patients
15.2	Demographics	Enrolled Patients
15.3	Baseline Characteristics	Enrolled Patients
15.4	Cancer History	Enrolled Patients
15.5	Abnormal Findings in Medical History	Enrolled Patients
15.6.1.1	Prior Leukemia Treatment by Therapeutic Class and Preferred Term	Enrolled Patients
15.6.1.2	Number of Prior Leukemia Treatment	Enrolled Patients
15.6.2	Best Response to Prior Leukemia Treatment	Enrolled Patients
15.7.1	Prior Medications by Therapeutic Class and Preferred Term	Safety Analysis Set
15.7.2	Prior hydroxyurea, Anagrelide, and Leukapheresis Usage by Therapeutic Class, and Preferred Term	Safety Analysis Set
15.8	Electrocardiogram Findings at Baseline	Enrolled Patients
15.9	Abnormal Physical Examination Findings at Baseline	Enrolled Patients
15.10	Protocol Violations	Enrolled Patients
15.11	Evaluation of Response (Adjudication) by Visit	Safety Analysis Set
15.12	Evaluation of Hematologic Response (Study Site Evaluation) by Visit	Safety analysis set
15.13	Evaluation of Cytogenetic Response (Study Site Evaluation) by Visit	Safety Analysis Set
15.14	Liver and Spleen Examinations by Visit	Safety analysis set
15.15	Bone Marrow Aspiration and Cytogenetics by Visit	Safety analysis set
15.16	Extramedullary Involvement data by Visit	Safety analysis set
15.17.1	Study Drug Exposure	Safety Analysis Set
15.17.2	Study Drug Exposure by Cycle	Safety Analysis Set
15.17.3	Study Drug Exposure – Cycle Delay	Safety Analysis Set
15.18.1	Summary of Treatment Emergent Adverse Events	Safety Analysis Set
15.18.2	Treatment Emergent Adverse Events by System Organ Class, Preferred Term	Safety Analysis Set
15.18.3	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Toxicity Grade	Safety Analysis Set
15.18.4	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Toxicity Grade – Grade 3 or Higher	Safety Analysis Set
15.18.5	Treatment-Related Treatment Emergent Adverse Events by System Organ	Safety Analysis Set

Summary number	Title	Population
	Class, and Preferred Term	
15.18.6	Treatment-Related Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Toxicity Grade	Safety Analysis Set
15.18.7	Serious Adverse Events by System Organ Class, and Preferred Term	Safety Analysis Set
15.18.8	Adverse Events Leading to Study Drug Withdrawal by System Organ Class and Preferred Term	Safety Analysis Set
15.18.9	Non-Serious Treatment Emergent Adverse Events by System Organ Class, and Preferred Term	Safety Analysis Set
15.19.1	Overall Worst NCI CTCAE (v4.0) Grades for Selected Hematology Laboratory Tests	Safety Analysis Set
15.19.2	NCI CTCAE (v4.0) Grades 3 or 4 for Selected Hematology Laboratory Tests by Cycle	Safety Analysis Set
15.20.1	Overall Worst NCI CTCAE (v4.0) Grades for Selected Chemistry Laboratory Tests	Safety Analysis Set
15.20.2	NCI CTCAE (v4.0) Grades 3 or 4 for Selected Chemistry Laboratory Tests by Cycle	Safety Analysis Set
15.21.1	Vital Signs Values and Changes From Baseline to Each Time Point and Endpoint	Safety Analysis Set
15.21.2	Vital Signs Clinically Significant Abnormal Values	Safety Analysis Set
15.22.1	Electrocardiogram Findings Shifts from Baseline to Each Time Point and Endpoint	Safety Analysis Set
15.22.2	Electrocardiogram Variables Results and Changes From Baseline to Each Time Point and Endpoint	Safety Analysis Set
15.23	ECOG Performance Status Changes From Baseline to Each Visit and Endpoint	Safety Analysis Set
15.24	Physical Examination Findings Shifts From Baseline to Each Visit and Endpoint	Safety Analysis Set
15.25.1	Medications by Therapeutic Class and Preferred Term	Safety Analysis Set
15.26.1	Plasma Concentration at Each Time Point - Omacetaxine	Pharmacokinetic Analysis Set
15.26.2	Plasma Concentration at Each Time Point - 4-DMHHT	Pharmacokinetic Analysis Set
15.26.3	Plasma Concentration at Each Time Point - Cephalotaxine	Pharmacokinetic Analysis Set
15.27.1	Pharmacokinetic Parameters- Omacetaxine	Pharmacokinetic Analysis Set
15.27.2	Pharmacokinetic Parameters- 4-DMHHT	Pharmacokinetic Analysis Set

10.2. Individual Patient Data Listings

Listing Number	Title	Population
16.2.1.01	Patient Disposition	Enrolled Patients
16.2.1.02	Patients Who Did Not Meet Screening Criteria	
16.2.2.01	Protocol Violations	Enrolled Patients
16.2.4.01	Demographics	Enrolled Patients
16.2.4.02	Medical History	Enrolled Patients
16.2.4.03	Cancer History	Enrolled Patients
16.2.4.04	Glucose History	Enrolled Patients
16.2.4.05	NYHA Functional Class	Enrolled Patients
16.2.4.06	Chest X-Ray	Enrolled Patients
16.2.4.07	Prior Leukemia Treatment	Enrolled Patients
16.2.4.08	Prior Leukemia Treatment – Assessment Date	Enrolled Patients
16.2.4.09	Prior Hydroxyurea/Anagrelide/Leukapheresis Usage	Enrolled Patients
16.2.5.01	Study Drug Administration (at Study Site)	Safety Analysis Set
16.2.5.02	Study Medication Record (from Patient's Diary)	Safety Analysis Set
16.2.6.01	Evaluation of Response	Enrolled Patients
16.2.6.02	Evaluation of Response by Study Site	Enrolled Patients
16.2.6.03	Liver Examination	Enrolled Patients
16.2.6.04	Spleen Examination	Enrolled Patients
16.2.6.05	Extramedullary Involvement	Enrolled Patients
16.2.6.06	Bone Marrow Aspiration and Cytogenetics	Enrolled Patients
16.2.6.07	Molecular Biology Data	Enrolled Patients
16.2.6.08	FISH (Fluorescence In Situ Hybridization) for Cytogenetic Analysis	Enrolled Patients
16.2.6.09	Follow-up	Enrolled Patients
16.2.7.01	Adverse Events	Enrolled Patients
16.2.7.02	Deaths	Enrolled Patients
16.2.7.03	Serious Adverse Events	Enrolled Patients
16.2.7.04	Adverse Events Causing Study Drug Withdrawn	Enrolled Patients
16.2.7.05	Adverse Events with NCI CTCAE Toxicity Grade of 3 or Higher	Enrolled Patients
16.2.7.06	MedDRA Version 16.1 Dictionary Terms For Adverse Event Descriptions	
16.2.7.07	Adverse Event Preferred Terms and Patient Number	
16.2.8.08	Adverse Events for Patients Who Did Not Meet Screening Criteria	
16.2.8.01	Laboratory Reference Ranges	

Listing Number	Title	Population
16.2.8.02	Serum Chemistry Laboratory Tests Results	Enrolled Patients
16.2.8.03	NCI CTCAE Grade 3 or 4 Serum Chemistry Laboratory Tests Results	Enrolled Patients
16.2.8.04	Hematology Laboratory Tests Results	Enrolled Patients
16.2.8.05	NCI CTCAE Grade 3 or 4 Hematology Laboratory Test Results	Enrolled Patients
16.2.8.06	Urinalysis Laboratory Tests Results	Enrolled Patients
16.2.8.07	Pregnancy Test Results (Females Only)	Enrolled Patients
16.2.8.08	Treatment Schedule	Enrolled Patients
16.2.8.09	Vital Signs Values	Enrolled Patients
16.2.8.10	Vital Signs Clinically Significant Abnormal Values	Enrolled Patients
16.2.8.11	Electrocardiogram Findings	Enrolled Patients
16.2.8.12	Electrocardiogram Variable Results	Enrolled Patients
16.2.8.13	Physical Examination Findings	Enrolled Patients
16.2.8.14	Performance Status (ECOG)	Enrolled Patients
16.2.8.15	Medications	Enrolled Patients
16.2.8.16	Hydroxyurea/Anagrelide/Leukapheresis Usage	Enrolled Patients
16.2.8.17	Concomitant Blood and Platelet Transfusion	Enrolled Patients
16.2.8.18	Pharmacokinetic Sample Times – Plasma	Pharmacokinetic Analysis Set
16.2.8.19	Pharmacokinetic Parameters	Pharmacokinetic Analysis Set

STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: C41443/2057

Study Title: 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

Statistical Analysis Plan for:

☐ Interim Analysis
X Final Analysis
☐ Integrated Summary of Efficacy
☐ Integrated Summary of Safety

Version: 1

Date: 03/28/2018

Author: [redacted]

Approver: [redacted] Apr 11, 2018
Date

Approver: [redacted] APRIL 12, 2018
Date