CLINICAL STUDY PROTOCOL

A Phase II Trial of High-dose Bendamustine, Etoposide, Cytarabine, and Melphalan (BeEAM) in the Up-front Treatment of Multiple Myeloma

Indication: Multiple Myeloma, following induction therapy

Phase: Phase II

Protocol History

Original	29Sept2014
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This is an investigator-initiated study. The principal investigator Scott R. Solomon, MD, (who may also be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

PROTOCOL SUMMARY

Study Title: A Phase II Trial of High-dose Bendamustine, Etoposide, Cytarabine, and Melphalan (BeEAM) in the Up-front Treatment of Multiple Myeloma

Phase: II

Number of Patients: 65

Study Objectives

Primary

- To estimate the response at day 100 following transplant.

Secondary

- To obtain estimates of overall survival (OS), event-free survival (EFS), and non-relapse mortality (NRM).
- Characterize the hematologic and non-hematologic toxicities of high-dose bendamustine when given as part of the BeEAM preparative regimen prior to autologous stem cell transplantation.

Overview of Study Design:

High-dose chemotherapy and autologous stem cell transplantation (ASCT) as part of the up-front treatment of patients with multiple myeloma has been associated with improved disease-free and overall survival in multiple large randomized controlled trials. Following 3-6 cycles of standard induction therapy with biologic agents, consolidation with high dose Melphalan and ASCT has become the standard-of-care approach for fit myeloma patients up to 70 years of age. Single-agent high-dose Melphalan ($200mg/m^2$) is currently the standard-of-care preparative regimen prior to autologous transplant in Myeloma. Historical studies utilizing Busulfan- or Total Body Irradiation-based preparative regimens have yielded similar results to single-agent Melphalan with higher toxicity.

Achievement of a complete response (CR) following autologous transplant for myeloma has been associated with improved disease-free and overall survival in multiple studies[1-5]. Therefore, more efficacious high-dose chemotherapy regimens that improve post-transplant CR rates should translate into better survival for myeloma patients. The regimen BeEAM, utilizing high-dose bendamustine, etoposide, cytarabine, and melphalan, has been utilized successfully in older lymphoma patients with excellent activity (80% CR rate), acceptable morbidity and no treatment-related mortality[6]. Bendamustine is an active agent in the treatment of multiple myeloma[7]. We hypothesize that incorporation of bendamustine in the high-dose preparative regimen will translate into better quality and more durable responses in myeloma patients.

Myeloma patients, following up-front induction therapy, will receive an ASCT following a high-dose bendamustine-based preparative regimen (BeEAM). The primary endpoint of this trial will be the rate of CR at day 100 post-transplant. Experience from the literature, as well as results from our institution, suggests that following ASCT for the upfront treatment of myeloma, the rate of CR at day 100 post-transplant is approximately 45%. It is hoped that under this protocol, this rate will be at least 65%. Thus we statistically formalize this study by testing the null hypothesis that p, the CR rate is 0.65 or more versus the alternative hypothesis that p is less than 0.45. A sample size of 65 pts gives 90% power with an alpha=0.05, using the formula for a one sample binomial (two-sided) test

of a proportion.
Study Population: Eligible patients will be 18 – 70 years of age, with adequate performance status and organ function, and have a diagnosis of multiple myeloma, within 9 months of the start of induction therapy.
Duration of Study: # months from FPI to LPI: 24 months # months from LPI to LPO: 3 months. # months to complete study: 27 months
Study Drug: Bendamustine will be provided by Teva Pharmaceuticals for purposes of this study.

SCHEDULE OF EVENTS

Test	Screen	Daily through D21*	Weekly D21-42*	Month 3 (Day 100)	Month 6	Month 12
H & P	X	X	X	X	X	X
CBC with differential	X	X	x	X	X	X
Chemistry	X	X	X	X	X	X
Myeloma Assessments (SPEP, UPEP, SIFE, UIFE, Free Kappa Light Chains, Immunoglobulins)*	X			X	X	X
Myeloma Residual Disease Assessment*	X			X		
PFT	X					
ECHO	X					
EKG	X					
IDMs including Hepatitis & HIV	X					
Pregnancy test (FOCBP)	X					
Toxicity Assessment		X	X	X	X	
Bone marrow biopsy & aspirate	X			X	X	X
Bone Survey	x			X	X	X
Survival						
New malignancy assessment						

**per standard of care*

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1.0 BACKGROUND AND STUDY RATIONALE

1.1 Introduction

Multiple myeloma (MM) is a clonal plasma cell disorder characterized by lytic bone disease, renal dysfunction, abnormal hematopoietic function, and the presence of a monoclonal paraprotein in the blood and/or urine. Historical induction regimens rarely achieved major responses [very good partial remission (VGPR) or complete remission (CR)], and before the use of high-dose therapy (HDT) and autologous stem cell transplantation (ASCT), few therapeutic options showed significant improvements in overall survival (OS) for newly diagnosed myeloma patients[1,2]. Over the last several decades, the treatment of MM has improved strikingly. Although not curative, autologous stem cell transplantation (ASCT) improves the likelihood of a complete response (CR), prolongs progression-free survival (PFS) and overall survival (OS), and represents a major advance in MM therapy.

Led first by the Intergroupe Francophone du Myelome (IFM), several groups have now shown improvements in survival for patients randomized to receive HDT when compared with conventional dose chemotherapy[3], rendering HDT a standard treatment approach for younger patients with newly diagnosed MM. In addition, the IFM has shown that achievement of a VGPR is a surrogate for improvement in PFS and OS[4], adding it as a new category in the revised International Myeloma Working Group response criteria[5]. CR is a prerequisite for tumor control and eventual cure in most, if not all, hematologic malignancies. CR rates in myeloma have improved substantially with stem cell transplantation. Improving CR rates is felt to be an important surrogate for the long-term goal of improving survival in myeloma. Achievement of CR following autologous transplant for myeloma has been associated with improved disease-free and overall survival in multiple studies[6-10].

Despite these improvements, patients are rarely, if ever, cured of MM through the use of HDT. To improve the efficacy of the HDT maneuver itself, groups have explored the use of multiple cycles of HDT (tandem transplant[11-13]), the use of combination chemotherapy conditioning regimens using agents in addition to or replacing melphalan in HDT conditioning[14-17], and the addition of radiation therapy using targeted antibodies[18-19] or external beam radiation[20]. Unfortunately, none of these approaches has been shown to be superior to the use of 200 mg/m^2 of melphalan. Thus, if we are to improve on the efficacy of HDT, alternative combination approaches are needed.

1.2 Anti-myeloma effect of Bendamustine

Bendamustine is a novel bifunctional alkylating agent consisting of three structural elements: a 2-chloroethylamine alkylating group; a butyric acid side chain; and a benzimidazole ring. Although its precise mechanism of action is as yet unknown, it appears to exert its antineoplastic effects via a different mechanism to those of other alkylating agents. Bendamustine has demonstrated significant efficacy in patients with indolent lymphomas and chronic lymphocytic leukemia (CLL), including in patients with disease refractory to conventional alkylating agents and rituximab. The toxicity profile of bendamustine is also superior to that of conventional alkylating agents. Bendamustine has promising activity in multiple myeloma (MM)[21-25]. Bendamustine seems to be efficacious either in monotherapy or in combination with other drugs in previously treated or untreated patients. Moreover, it has an acceptable toxicity profile and is suitable for patients with renal impairment. It is currently licensed in Europe for use as frontline treatment with prednisolone for patients with MM who are unsuitable for transplantation and who are contraindicated for thalidomide and bortezomib therapy.

1.3 Rationale for use of Bendamustine in HDT/ASCT

Given the efficacy and favorable safety profile of bendamustine, it is natural to explore this drug in the HDT/ASCT setting. In the setting of relapsed/refractory lymphoma, Visani and colleagues performed a phase 1-2 study to test the safety and the efficacy of increasing doses of bendamustine, coupled with fixed doses of etoposide, cytarabine, and melphalan (BeEAM), in the conditioning regimen prior to ASCT for resistant/relapsed lymphoma patients[26]. Forty-three patients (median age, 47 years) with non-Hodgkin (n = 28) or Hodgkin (n = 15) lymphoma were consecutively treated. Nine patients entered the phase 1 study; no patients experienced a dose-limiting toxicity. Thirty-four additional patients were then treated in the phase 2 study. All patients engrafted, with a median time to absolute neutrophil count > 0.5 x 10(9)/L of 10 days. The 100-day transplantation-related mortality was 0%. After a median follow-up of 18 months, 35 of 43 patients (81%) were in complete remission, whereas 6 of 43 relapsed and 2 of 43 did not respond.

1.4 Potential Risks and Benefits

Bendamustine

Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells. The exact mechanism of action of bendamustine remains unknown. The drug is 94%–96% bound to plasma proteins, and is primarily metabolized via hydrolysis to non-cytotoxic metabolites. Two minor active metabolites are formed via CYP1A2. Bendamustine does not induce nor inhibit CYP metabolic pathways.

Approximately 90% of the administered drug is recovered from the excreta, primarily feces. Bendamustine is currently FDA approved for the treatment of patients with chronic lymphocytic leukemia and indolent non-Hodgkin's lymphoma. Bendamustine has promising activity in multiple myeloma and is currently licensed in Europe for use as frontline treatment with prednisolone for patients with MM who are unsuitable for transplantation and who are contraindicated for thalidomide and bortezomib therapy. Most common adverse reactions are neutropenia, anemia, thrombocytopenia, lymphopenia, nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight loss, dyspnea, rash, and stomatitis.

Etoposide

Etoposide is a semisynthetic derivative of the podophyllotoxins, an epipodophyllotoxin. It inhibits DNA topoisomerase II, thereby inhibiting DNA synthesis. Etoposide is cell cycle dependent and phase specific, affecting mainly the S and G2 phases. Etoposide is metabolized in the liver via the cytochrome p450 system (CYP3A4 involved). Elimination is described by two compartment open model, with the primary route of elimination being renal. Biliary excretion accounts for up to 44% recovery in feces. Etoposide is currently FDA approved in the treatment of testicular cancer and small cell lung cancer. Most common adverse reactions are neutropenia, anemia, thrombocytopenia, nausea, vomiting, diarrhea, stomatitis, esophagitis, hypotension, alopecia, hepatic toxicity, and allergic reactions.

Cytarabine

Cytarabine is an antineoplastic agent. Cytarabine is a synthetic pyrimidine nucleoside, which is converted intracellularly to the nucleotide, cytarabine triphosphate. The exact mechanism of action of cytarabine is not fully understood, but cytarabine triphosphate appears to inhibit DNA

synthesis by the inhibition of DNA polymerase. Cytarabine's actions are cell-cycle specific. Cytarabine is rapidly metabolised, mainly in the liver, to the inactive metabolite 1-β-D-arabinofuranosyluracil. About 70 to 80% of a dose is excreted in the urine within 24 hours; approximately 90% as the metabolite and 10% as unchanged cytarabine. Cytarabine in combination with other approved anticancer drugs is indicated for remission induction in acute non-lymphocytic leukemia of adults and children. It has also been found useful in the treatment of acute lymphocytic leukemia and the blast phase of chronic myelocytic leukemia. Most common adverse reactions are neutropenia, anemia, thrombocytopenia, nausea, vomiting, diarrhea, stomatitis, alopecia, skin rash, and conjunctivitis.

Melphalan

Melphalan, a bifunctional nitrogen mustard-derivative alkylating agent, is the L-isomer of mechlorethamine. Melphalan inhibits DNA and RNA synthesis via formation of interstrand cross-links with DNA, likely binding at the N7 position of guanine. Melphalan is cell cycle phase-nonspecific. Melphalan does not undergo metabolic activation and is inactivated in the plasma, primarily by non-enzymatic hydrolysis to monohydroxymelphalan and dihydroxymelphalan. At conventional intravenous dosage, melphalan is indicated in the treatment of multiple myeloma and ovarian cancer. At high intravenous dosage, it is indicated, with or without hematopoietic stem cell transplantation, for the treatment of multiple myeloma and childhood neuroblastoma. Most common adverse reactions are neutropenia, anemia, thrombocytopenia, nausea, vomiting, diarrhea, stomatitis, esophagitis, and alopecia.

Regimen-related toxicities

Toxicities directly related to the administration of high-dose chemotherapy include gastrointestinal toxicity (nausea, vomiting, mucositis), alopecia, infertility (which may be permanent), interstitial pneumonitis, idiopathic cardiomyopathy, hepatic sinusoidal obstruction syndrome, or multi-organ failure which may be fatal.

Infection

Infection is a major cause of morbidity in ASCT and is a major concern in these patients. Infections may be bacterial, viral, parasitic, or fungal. Often, these infections are life-threatening, particularly when caused by viral or fungal organisms, and are associated with high mortality in the transplant population.

Reproductive Considerations

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and must permanently discontinue study drug. This also applies to male patients whose partners become pregnant while the patient is on study or within the 12 week period after last dose of study drug. Patients of reproductive potential (males and females) must practice double-barrier methods of contraception during treatment and for 12 weeks following the last dose of Bendamustine. Adequate contraception is defined as double-barrier protection (i.e., condom plus spermicide in combination with a diaphragm, cervical/vault cap, or intrauterine device). Birth control pills, birth control patches and/or injections of hormones or (in males) surgical sterilization (i.e., status post-vasectomy) to prevent pregnancy are not considered an adequate method of preventing pregnancy, and double-barrier protection is

required while on study and for 12 weeks after last dose, or the patient must completely abstain from heterosexual intercourse.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

- To estimate the response at day 100 following transplant.

2.2 Secondary Objectives

- To obtain estimates of overall survival (OS), event-free survival (EFS), and non-relapsed mortality (NRM).
- Characterize the hematologic and non-hematologic toxicities of high-dose bendamustine when given as part of the BeEAM preparative regimen prior to autologous stem cell transplantation.

3.0 STUDY DESIGN

3.1 Overview of Study Design

Patients will be required to meet institutional guidelines for transplantation and follow the institutional standard for post-transplant care. At a minimum, patients will need to be seen for study related purposes according to the following schedule. Other tests and exams will be done according to physician preference.

Test	Screen	Daily through D21*	Weekly D21-42*	Month 3 (Day 100)	Month 6	Month 12
H & P	X	X	X	X	X	X
CBC with differential	X	X	x	X	X	X
Chemistry	X	X	X	X	X	X
Myeloma Assessments (SPEP, UPEP, SIFE, UIFE, Free Kappa Light Chains, Immunoglobulins)*	X			X	X	X
Myeloma Residual Disease Assessment*	X			X		
PFT	X					
ECHO	X					
EKG	X					
IDMs including Hepatitis & HIV	X					
Pregnancy test (FOCBP)	X					
Toxicity Assessment		X	X	X	X	
Bone marrow biopsy & aspirate	X			X	X	X
Bone Survey	x			X	X	X
Survival						
New malignancy assessment						

**per standard of care*

3.2 Number of Patients

Sixty-five (65) patients will be enrolled on this study. Should a patient sign consent and not be transplanted, they will be considered a screen failure and replaced.

3.3 Duration of Study

Adverse events will be collected for 30 days post-transplant. Patients will be followed for disease status and survival at 3, 6 and 12 months post-transplant. All other follow-up will be done per institutional guidelines and data will be collected form the BMT database to analyze progression free and overall survival.

4.0 STUDY POPULATION

4.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Age between 18 - 70 years
2. Karnofsky status ≥ 70%
3. Diagnosis of Multiple Myeloma
4. Within 9 months of the start of induction chemotherapy and no evidence of relapse or progression.
5. Availability of Cryopreserved peripheral blood stem cells with a CD34 dose of at least $2x10^6$/kg.

4.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Patients will not be excluded on the basis of sex, racial or ethnic background.
2. Poor cardiac function: left ventricular ejection fraction <40%
3. Poor pulmonary function: FEV_1, FVC, or DLCO <40% predicted

4. Poor liver function: bilirubin ≥2.5 mg/dl (not due to hemolysis, Gilbert's or primary malignancy), AST/ALT > 3X ULN
5. Poor renal function: Creatinine ≥2.0 mg/dl or creatinine clearance < 40 mL/min (calculated creatinine clearance is permitted)
6. Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.
7. Women of childbearing potential who currently are pregnant or who are not practicing adequate contraception
8. Patients who have any debilitating medical or psychiatric illness which would preclude their giving informed consent or their receiving optimal treatment and follow-up.

5.0 TREATMENT PLAN / STUDY DRUG

5.1 Transplant Regimen

Preparative Regimen

Days –7, -6 Bendamustine 200 mg/m2/day for 2 days

↓

Days –5→ -2 cytarabine, 400 mg/m2/day for 4 days

etoposide, 200 mg/m2/day for 4 days

↓

Day –1 Melphalan 140 mg/m2

Chemotherapy Dosing:

All chemotherapy should be dosed based on ideal body weight (IBW) for patients who weigh 100-130% of their IBW. For patients who weigh less than 100% of their IBW, dosing should be based on actual body weight (ABW). For patients who weigh more than 130% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW). .

- Ideal Body Weight (IBW) Formulas:

  Males IBW = 50 kg + 2.3 kg/inch over 5 feet

  Females IBW = 45.5 + 2.3 kg/inch over 5 feet

  For patients less than 5 feet, subtract 2.3 kg/inch

- Adjusted Ideal Body Weight (AIBW) Formula:

  AIBW = IBW + [(0.25) x (ABW – IBW)]

Dosing Adjustments:

CHEMOTHERAPEUTIC AGENT	Adjustment for Renal Insufficiency (GFR in ml/min) *Percentage of normal dose	
	60 - 51	≤50
Etoposide	100%	75%

CHEMOTHERAPEUTIC AGENT	Adjustment for Hepatic Dysfunction % of Standard Dose To Be Administered						
	T.Bili < 1.5	AST < 60	T.Bili 1.5-3.0	AST 60-180	T.Bili 3.1-5	AST > 180	T. Bili > 5.0
Bendamustine	100%		Omit if AST/ALT ≥2.5xULN or T. Bili ≥1.5xULN				
Etoposide	100%		50%		omit		omit

Growth factor support: Patients will receive G-CSF (Filgrastim) 5 mcg/kg/d SQ starting day +6 and continuing until the ANC >1000/mm^3 x 3 days or 1500/mm^3 x 1 day.

Supportive Care: Antibiotic prophylaxis and other supportive care measures will be implemented according to institutional guidelines.

6.0 STATISTICAL AND QUANTITATIVE ANALYSES

6.1 Statistical Methods

6.1.1 Determination of Sample Size

The primary endpoint of this trial will be the rate of CR at day 100 post-transplant. Experience from the literature, as well as results from our institution, suggests that following ASCT for the upfront treatment of myeloma, the rate of CR at day 100 post-transplant is approximately 45%. It is hoped that under this protocol, this rate will be at least 65%. Thus we statistically formalize this study by testing the null hypothesis that p, the CR rate is 0.65 or more versus the alternative hypothesis that p is less than 0.45. A sample size of 65 pts gives 90% power with an alpha=0.05, using the formula for a one sample binomial (two-sided) test of a proportion. We expect that patients will be accrued over 2 years.

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

7.1.2 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

Adverse events will be collected from the time the patient signs the informed consent and ends 30 days after the discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time.

7.1.3 Serious Adverse Event Reporting

The investigator will comply with all safety reporting regulations as set forth in the Code of Federal Regulations. The investigator being the sponsor of the study has the sole responsibility for reporting all serious adverse events to the Northside Hospital Institutional Review Board (the IRB of record), TEVA pharmaceuticals and if serious and either likely, possibly, probably, or definitely related to study drug to the FDA. For informational purposes any correspondence to the FDA regarding adverse events or other safety issues will be simultaneously copied to us.clinops.sae@tevapharm.com or reported to Teva via facsimile at 215-619-3825. The

investigator will communicate the occurrence of serious adverse events to Teva and the IRB of record within 24 hours of becoming aware of the event. Reporting of Adverse Events to Teva does not preclude the responsibility of the investigator to report adverse events to the FDA.

7.1.4 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible

Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

- Results in a development of drug dependency or drug abuse
- Is a serious adverse drug experience

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

7.2 Procedures for Reporting Serious Adverse Events

The following AEs will be reported to the Northside Hospital Institutional Review Board, from the date the participant receives the first dose of study drug through 30 days after administration of the last dost of Bendamustine:

· Grade 1 adverse events do not need recorded

· Grade 2 unexpected **and** probably/definitely related

· All non-hematologic grades 3, 4 & 5 possibly/probably/definitely related

Any SAE that occurs at any time during treatment with Bendamustine or for 30 days after the completion of Bendamustine treatment that the sponsor-investigator and/or sub-investigator

considers to be possibly/probably/definitely related to the study drug must be reported to Northside Hospital Institutional Review Board. The investigator must notify Teva of any serious adverse events that may occur after this time period which the investigator believes to be definitely, likely or possibly related to the study product.

Additionally, the following will also be deemed to be adverse events for purposes of this study; pregnancy exposure, infant exposure during breastfeeding, overdose, abuse, misuse, medication errors, lack of efficacy, infectious agents, as well as all reports of accidental pediatric exposure and other safety information as reasonably requested by the sponsor. In the event the IRB requests additional safety information from the investigator, investigator will notify Teva of such request within one (1) business day.

New primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered SAEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). A visit to the hospital emergency room or hospital clinic would not be considered inpatient hospitalization; however, it could be considered serious if medical intervention was necessary in order to prevent a serious outcome. It should be noted that disease progression, and death due to disease progression will be considered clinical endpoints for the study, and will not be considered serious adverse events.

All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

8.0 ADMINISTRATIVE REQUIREMENTS

8.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

8.2 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Teva requests that informed consent documents be reviewed by Teva or designee prior to IRB/IEC submission.

8.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

8.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

8.5 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Teva and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Teva and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

8.6 On-site Audits

Regulatory authorities, the IEC/IRB and/or Teva may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

8.7 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

8.8 Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Teva, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Teva by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the drug

8.9 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s).

8.10 Study Drug

Bendamustine will be provided by Teva Pharmaceuticals for purposes of this clinical research study.

9 USE OF INFORMATION

All information regarding Bendamustine supplied by Teva to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Teva. It is understood that there is an obligation to provide Teva with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of Bendamustine and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Teva, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

10 REFERENCES

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