SeattleGenetics

Protocol Number:	SGN33A-003
Version:	Amendment 3; 15-Mar-2017
Protocol Title:	A phase 1/2 study of vadastuximab talirine administered in sequence with allogeneic hematopoietic stem cell transplant in patients with relapsed or refractory acute myeloid leukemia (AML)
Investigational Drug:	Vadastuximab talirine (SGN-CD33A)
Indication:	Acute myeloid leukemia
Phase:	1/2
IND Number:	116300
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PROTOCOL SYNOPSIS

Protocol Number SGN33A-003 **Version** Amendment 3 **Phase** Phase 1/2	**Product Name** Vadastuximab talirine (SGN-CD33A) **Sponsor** Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

A phase 1/2 study of vadastuximab talirine administered in sequence with allogeneic hematopoietic stem cell transplant in patients with relapsed or refractory acute myeloid leukemia (AML)

Study Objectives

Primary

- Phase 1
  - To assess the safety and tolerability of vadastuximab talirine
  - To determine the recommended dosing levels of vadastuximab talirine pre- and post-allogeneic hematopoietic stem cell transplant (alloSCT)
- Phase 2
  - To assess the 1-year survival rates of patients treated with vadastuximab talirine at the recommended doses pre- and post-alloSCT
  - To assess the rate of minimal residual disease (MRD) negativity at Day −1 pre-transplant and Day 30 post-transplant (Part A only)
  - To assess the safety and tolerability of vadastuximab talirine at the recommended dosing levels

Secondary

- To assess the best response on study treatment (Part A only)
- To assess the duration of response (Part A only)
- To assess overall survival (OS)

Additional

- To assess the pharmacokinetics, antitherapeutic antibodies (ATA), and pharmacodynamics of vadastuximab talirine
- To assess event-free survival (EFS)
- To assess the rate of MRD negativity
- To assess lymphocyte subset recovery after alloSCT
- To assess CD33 expression levels and post-treatment target (CD33) saturation
- To assess biomarkers of biological activity, resistance, and outcome

Study Population

Eligible patients must have AML (acute promyelocytic leukemia (APL) is excluded). Patients must be 18 to 75 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and have adequate baseline renal, hepatic, cardiac, and pulmonary function. Patients with central nervous system leukemia are not permitted in the study. Patients with any uncontrolled Grade 3 or higher ongoing infection prior to the first dose of study drug will not be eligible; however, prophylaxis or treatment for

resolving/controlled infection is acceptable. Patients with documented history of cerebral vascular events will be excluded. Patients may not participate if they have known hypersensitivity to excipients contained in the drug formulations of vadastuximab talirine, fludarabine, melphalan, tacrolimus, or methotrexate.

Part A

Patients enrolled in Part A, the pre-alloSCT arm, must have relapsed and/or refractory AML, have received 2 or 3 previous induction regimens including at least one intensive chemotherapy regimen, and be eligible to undergo an alloSCT. Patients enrolled in Part A will not be eligible to enroll in Part B.

Part B

Patients enrolled in Part B must have successfully undergone an alloSCT for relapsed or refractory AML and achieved a CR or CR with incomplete blood count recovery (CRi). Patients must be without significant graft-versus-host disease (GVHD) and without a history of veno-occlusive disease (VOD) requiring defibrotide.

Number of Planned Patients

Approximately 102 patients are expected to participate in the study.

Part A

Phase 1 will enroll approximately 18 patients and Phase 2 will enroll up to 36 patients. An additional 36 patients may be added to Phase 2 of Part A if exploration of an alternative dose is desired.

Part B

Phase 1 will enroll approximately 12 patients. Phase 2 will enroll up to 36 patients.

Study Design

This is a 2-part study to evaluate the safety and activity of vadastuximab talirine in patients with relapsed chemo-resistant AML: Part A will examine vadastuximab talirine in cytoreduction pre-conditioning and Part B will examine vadastuximab talirine in post-alloSCT maintenance. Each study part will consist of a phase 1 safety evaluation followed by a phase 2 expansion for efficacy. Parts A and B will enroll concurrently. Phase 2 will be initiated following dose level recommendation by the Safety Monitoring Committee (SMC) with the determination of the MTD or recommended phase 2 doses for Parts A and B, and an evaluation of the overall safety profile. At the discretion of the SMC, dose levels may be expanded in phase 1. All patients will be followed for survival status until 5 years after the last patient is enrolled, or until study closure, whichever occurs first.

An SMC consisting of the study medical monitor, investigators, and the study biostatistician will monitor the safety of patients treated with vadastuximab talirine on a regular basis throughout the study, including reviews of the data pertinent to dose-escalation decisions and evaluation of potential cumulative toxicity. The SMC may recommend investigation of an intermediate dose level during dose escalation. Dose levels for expansion will be selected by the sponsor in consultation with the SMC, based on known safety and activity data.

Part A

One dose of vadastuximab talirine will be administered intravenously on Day −14 for patients in the cytoreduction pre-conditioning part followed by reduced intensity chemotherapy (RIC) of melphalan and fludarabine on Days −5 to −2. AlloSCT will be performed on Day 0.

Patients will be evaluated for response at Day 30, and every 3 months from transplant for 1 year and then every 6 months until 3 years post-transplant.

Part A phase 1 of the study will be conducted using a standard 3+3 design. Part A phase 2 of the study will be an open-label, non-randomized study conducted with doses of vadastuximab talirine at or below the MTD established in phase 1.

Part B

In Part B, patients will enter the study between 42 and 100 days after the alloSCT and will receive vadastuximab talirine on Day 1 of 42-day cycles for up to 12 months.

Response assessments will be every 3 months after the first dose of study drug for 2 years (every other cycle during treatment), and then every 6 months until 3 years post-transplant. Patients in Part B who discontinue study treatment prior to relapse will be evaluated for response until progression or initiation of new anticancer treatment, whichever comes first.

Part B phase 1 of the study will treat 6 patients at Dose Level 1 (10 mcg/kg) beginning between 42 and 100 days post transplantation. In the event of dose-limiting toxicity (DLT) occurring in 2 or more patients, 6 additional patients will be treated at a lower Dose Level –1 (5 mcg/kg).

Test Product, Dose, and Mode of Administration

Part A

Vadastuximab talirine at escalating doses starting at 40 mcg/kg will be administered IV push without routine premedication on Day –14 for Part A.

Pre-alloSCT RIC

- Fludarabine 30 mg/m^2/day IV on Day –5 to Day –2 (total dose of 120 mg/m^2)
- Melphalan 140 mg/m^2 IV on Day –2

GVHD prophylaxis

- Tacrolimus 0.03 mg/kg/day IV (initial dose Day –1); subsequent oral or IV doses target blood trough levels 5–15 ng/mL
- Methotrexate 5–10 mg/m^2 Day 1 and 5 mg/m^2 IV on Days 3, 6, and 11 post-transplant

Part B

Vadastuximab talirine at 5–10 mcg/kg will be administered IV push without routine premedication on Day 1 of 42-day cycles for Part B.

Duration of Treatment

Part A

Patients in Part A will receive 1 dose of vadastuximab talirine.

Part B

Patients in Part B will receive vadastuximab talirine on Day 1 of 42-day cycles for up to 8 cycles. Patients who derive clinical benefit may continue treatment for up to 8 additional cycles with medical monitor approval.

Efficacy Assessments

Response categorization will be based on the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia (Cheson 2003). MRD will be assessed at a central laboratory by multiparametric flow cytometry of bone marrow samples according to the Research Specimen Manual (Walter 2011).

Pharmacokinetic and Immunogenicity Assessments

Blood samples for PK and ATA assessment will be collected at protocol-specified time points. Sensitive, qualified assays will be used to measure concentrations of ADC (vadastuximab talirine), and SGD-1882 in plasma and ATA in serum. Remaining PK samples will be archived for possible analysis of vadastuximab talirine -related species. The assays will include enzyme-linked immunosorbent assays (ELISA) and LC-MS/MS assays, as well as other assays if further characterization is required. A qualified electrochemiluminescence assay will be used to assess ATA.

Biomarker Assessments

Part A

Peripheral blood and bone marrow aspirates will be collected at the time points outlined in Table 4 and Table 5. Biomarker assessments in Part A may include CD33 expression level and saturation by vadastuximab talirine on CD33+ cells, cytogenetic abnormalities and/or mutation of genes with known prognostic significance for AML, soluble CD33, lymphocyte subset recovery post-transplant and evaluation of MRD at protocol specified time points outlined in Table 4 and Table 5.

Part B

Peripheral blood and bone marrow aspirates will be collected at the time points outlined in Table 6. Part B assessments may include soluble CD33, evaluation of MRD, and lymphocyte subset recovery post-transplant to monitor changes that may be associated with long term treatment with vadastuximab talirine.

Safety Assessments

Safety assessments will consist of the surveillance of AEs, laboratory test measures, physical examination findings, and concomitant medication records. Complete blood count (CBCs) and serum chemistries will be obtained regularly. GVHD will be assessed using GVHD Target Organ Staging (Harris 2016).

Determination of Sample Size

Phase 1 of Part A follows the 3+3 dose-escalation design. It is anticipated that 18 patients will be treated. Phase 1 of Part B follows a dose de-escalation design with 6 patients in each of the 2 planned dose levels. It is anticipated that 12 patients will be treated.

The sample size of Phase 2 of each part of the study is based on the one-year survival rate. The statistical hypotheses are

H_0: One-year survival rate < 20%, vs H_1: One-year survival rate ≥ 20%.

Assuming that the true one-year survival rate is 40%, a sample size of 36 will provide 83% power at a one-sided significance level of 5% using exact binomial test.

Statistical Methods

Study measures of safety, PK, baseline biomarkers, pharmacodynamic biomarkers, and efficacy will be summarized by descriptive statistics. The all treated patients analysis set will include patients treated with any amount of vadastuximab talirine. The DLT-evaluable analysis set includes all treated patients who either experienced a DLT or were followed for the full DLT evaluation period. All efficacy and safety analyses will be based on the all treated patients analysis set. The one-year survival rate and its 95% confidence interval will be estimated by Kaplan-Meier method. OS, duration of response and EFS will be analyzed using Kaplan-Meier method. Median OS, duration of response, and EFS will be calculated, where possible, with 95% confidence intervals. Each part of the study will be summarized independently.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
alloSCT	allogeneic stem cell transplant
AML	acute myeloid leukemia
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
AUC	area under the concentration-time curve
β-hCG	beta human chorionic gonadotropin
C_{eoi}	concentration at the end of infusion
C_{max}	maximum concentration
CR	complete remission
CRi	complete remission with incomplete blood count recovery
C_{trough}	trough concentration
CBC	complete blood count
CRF	case report form
DLI	donor lymphocyte infusion
DLT	dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOT	end of treatment
GCP	good clinical practice
GVHD	graft-versus-host disease
ICH	International Conference on Harmonization
IEC	independent ethics committee
IRB	institutional review board
IND	Investigational New Drug
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PD	progressive disease
RIC	reduced intensity chemotherapy
SAE	serious adverse event
SAP	statistical analysis plan
SMC	safety monitoring committee
SOS	Sinusoidal obstruction syndrome
TLS	Tumor lysis syndrome
ULN	upper limit of normal
VOD	veno-occlusive disease

1 INTRODUCTION

1.1 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a bone marrow malignancy defined by the dysregulation of differentiation and proliferation of hematopoietic progenitor cells. This results in the uncontrolled proliferation of immature malignant blasts and a deficiency in normal cells including red blood cells, normal white blood cells, and platelets. If untreated, AML generally causes death in weeks to months due to infection, bleeding, or complications related to leukostasis. In 2014, it was estimated that approximately 18,000 new cases of AML would be diagnosed in the United States, and about 10,000 deaths due to AML would occur in that same year (ACS 2012). The prognosis for AML depends heavily on factors such as patient age, cytogenetic and molecular abnormalities, and antecedent myelodysplasia.

For patients who are age 60 years or younger with newly diagnosed AML, or for relatively fit patients above the age of 60 years, standard of care generally consists of induction treatment with cytarabine continuous infusion x 7 days and with an anthracycline x 3 days (typically called "7+3") (Dohner 2015). Generally, the complete remission (CR) rate for these patients is approximately 65% (Mayer 1994); For patients achieving a CR, post-remission therapy has generally included repeated cycles of cytarabine-based chemotherapy or a hematopoietic stem cell transplant, either autologous, or more frequently an allogeneic transplant from an HLA-compatible donor (Dohner 2010). Despite achievement of CR, however, approximately 75% of these patients will experience disease relapse following initial induction therapy (Rollig 2011). For patients whose disease recurs after achieving a remission with induction, the treatment options are limited, with reported median survival of approximately 12 months or less (Leopold 2002). Accordingly, the development of new therapies for patients resistant to standard chemotherapeutic agents is clearly needed.

1.2 Allogeneic Transplant in AML

Outcomes for patients with relapsed and/or refractory AML remain poor (Breems 2005). An allogeneic transplantation is the only currently available curative treatment option for the majority of these patients. Transplant survival is significantly improved if patients achieve a complete hematologic remission prior to transplantation (Cornelissen 2012) and the standard of care at most institutions has been to attempt re-induction chemotherapy and perform transplantation if a subsequent remission is achieved. Unfortunately the rates of successful re-induction therapy overall remain low with only 20%–30% of patients responding to salvage regimens (Leopold 2002). Additional chemotherapy, especially if unsuccessful, often leaves patients weak and unfit to undergo further treatment including stem cell transplantation. Thus, despite the increasing availability of compatible donors, many patients are not transplanted because of the inability to achieve disease control prior to transplant.

An alternate strategy has been to identify those patients who are unlikely to benefit from salvage chemotherapy and perform an allogeneic transplant in the setting of active disease. Data from multiple studies have demonstrated that these patients can be readily identified using well validated clinical and laboratory variables (Estey 1997; Breems 2005; Chevallier

2011). Despite the toxicities associated with transplant, the administration of chemo/radiotherapy in conjunction with immuno-competent allogeneic donor cells has been shown to be capable of overcoming chemotherapy resistance (Biggs 1992). Most reported experiences using standard transplant conditioning regimens, have demonstrated that despite the achievement of remission in the majority of these chemotherapy-resistant patients, almost all relapse and die within one year of the transplant. Data from the CIBMTR as well as others have shown that the one year survival rates for transplants performed for AML in active disease are approximately 10% to 20% with very few long term survivors (Michallet 2000; Duval 2010).

An alternative strategy for preventing relapse post-transplant has been to administer additional antileukemic agents following successful engraftment of stem cells. Clinical trials in this setting have included the use of hypomethylating agents such as azacitidine (de Lima 2010) or tyrosine kinase inhibitors in patients with Flt-3 mutated AML (Chen 2014). These studies have demonstrated that it is feasible to give antileukemic therapy post-transplant.

1.3 CD33

CD33, also known as Siglec-3 or gp67, is a 67 kilodalton glycosylated transmembrane protein of the sialic acid binding sialoadhesin receptor (Siglec) family (von Gunten 2008; Jandus 2011). Like other family members, CD33 possesses aminoterminal V-set and C2-set immunoglobulin superfamily domains that facilitate binding to sialic acid as well as conserved, intracellular inhibitory signaling motifs (ITIM) (Cao 2011). Engagement of the receptor by ligand-binding or cross-linking leads to tyrosine phosphorylation of the ITIM region, recruitment and activation of Src-homology 2 (SH2)-containing phosphatases, Shp-1 or Shp-2, and endocytosis of the CD33-ligand complex (Ulyanova 1999; Paul 2000; Walter 2008; Sutherland 2009). Signaling through CD33 has been reported to mediate inhibitory signals that regulate intracellular calcium mobilization (Ulyanova 1999), cell adhesion (Taylor 1999), apoptosis of leukemic cells (Vitale 2001), myeloid cell maturation (Ferlazzo 2000), as well as production of cytokines (Sutherland 2009).

The CD33 antigen is present on the surface of malignant cells in the majority of patients with AML. In addition to myeloid and monocytic leukemia cells, CD33 is also expressed on normal committed myelomonocytic and erythroid progenitor cells and mature myeloid/monocytic cells, mast cells (Escribano 1998) and some NK cells (Eissens 2012) but is not thought to be expressed by the earliest pluripotent stem cells, on lymphoid cells or cells outside of the hematopoietic system (Sabbath 1985; Andrews 1986). Upon differentiation, CD33 is decreased on mature granulocytes but retained on macrophages, monocytes and dendritic cells (Buhring 1989).

1.3.1 CD33-Directed Therapies for AML

Several antibody-based therapies targeting CD33 have been evaluated in the clinic for the treatment of AML (FitzGerald 2011; Jurcic 2012). They include the anti-CD33 antibody huM195 (lintuzumab), AVE9633, an anti-CD33-maytansinoid drug conjugate (Lapusan 2012) and gemtuzumab ozogamicin (marketed as Mylotarg™), an anti-CD33 monoclonal

antibody conjugated to the cytotoxic agent calicheamicin. Lintuzumab was tested in clinical trials as a single agent, in combination with standard of care therapies, or conjugated to radionuclides (Feldman 2005; Raza 2009; Rosenblat 2010; Sekeres 2013). Overall, the effects were modest and insufficient benefit was demonstrated. Similarly, clinical development of AVE9633 was discontinued after a low level of activity was found against relapsed or refractory AML patients in 3 phase 1 trials (Lapusan 2012). In contrast, gemtuzumab ozogamicin was granted accelerated approval in 2000 for the treatment of relapsed AML, with an overall remission rate of approximately 30% in relapsed or refractory disease (Sievers 2001; Fenton 2005). A subsequent randomized phase 3 study in which a standard 7+3 induction regimen was compared to a reduced 7+3 regimen plus a single dose of gemtuzumab ozogamicin, failed to show improvement in outcome (Petersdorf 2013). Lack of benefit in this study, amidst concerns over increased deaths in the gemtuzumab ozogamicin arm, led to voluntary market withdrawal of the drug in 2010. Recent studies have demonstrated that a lower dose of gemtuzumab ozogamicin combined with standard induction chemotherapy may improve survival in patients with AML (Burnett 2011; Castaigne 2012). Taken together, these data help confirm validity of CD33 as a drug target, but suggest that an improved antibody-drug conjugate (ADC) with a favorable safety and toxicity profile is desirable (Jurcic 2012).

1.4 Vadastuximab talirine (SGN-CD33A)

Vadastuximab talirine (SGN-CD33A) is a CD33-directed ADC consisting of three functional subunits:

- An anti-CD33 antibody with an engineered cysteine residue in position 239 of each heavy chain (h2H12ec)
- A DNA-cross linking pyrrolobenzodiazepine dimer drug (SGD-1882)
- A protease-cleavable linker that covalently attaches SGD-1882 to h2H12ec

The antitumor activity and immunospecificity of vadastuximab talirine have been demonstrated in vitro and in vivo with models representing CD33-positive AML. A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects is provided in the Investigator's Brochure and preliminary results were reported (Stein 2014).

1.5 Rationale for Study

Preliminary results from the phase 1 trial of vadastuximab talirine in relapsed/refractory AML patients have demonstrated significant leukemic cell cytoreduction which was dose-dependent (Stein 2014). Blast clearance from the marrow was uncommon in patients receiving doses between 5 and 30 mcg/kg whereas in patients treated with 40–60 mcg/kg, approximately 50% of patients experienced blast clearance (mLFS, CRi or CR). Minimal residual disease (MRD) negativity was observed in the majority of patients who achieved a CR. No consistent pattern of off-target toxicity was observed. These preliminary data suggest that dose escalation, starting at 40 mcg/kg is appropriate in the setting of hematopoietic stem cell rescue without incurring excess extra-medullary toxicity and transplant-related complications. The administration of vadastuximab talirine could offer sufficient leukemic cell cytoreduction, prior to transplantation, with a resultant significant decrease in relapse rates in AML patients transplanted with active disease.

Results from the phase I trial with vadastuximab talirine have shown that patients achieving a complete remission have safely tolerated repeated low doses of therapy (5–10 mcg/kg) every 4 weeks. Since a high percentage of refractory/relapsed AML patients achieve a complete hematological remission following transplant for active disease, administration of vadastuximab talirine at low-doses post-transplant could also be used to help eradicate residual leukemic cells that remain and give rise to relapse.

2 OBJECTIVES

2.1 Primary Objective

- Phase 1
  - To assess the safety and tolerability of vadastuximab talirine
  - To determine the recommended dosing levels of vadastuximab talirine pre- and post-allogeneic hematopoietic stem cell transplant (alloSCT)
- Phase 2
  - To assess the 1-year survival rates of patients treated with vadastuximab talirine at the recommended doses pre- and post-alloSCT
  - To assess the rate of MRD negativity at Day –1 pre-transplant and Day 30 post-transplant in the pre-transplant portion of the study (Part A only).
  - To assess the safety and tolerability of vadastuximab talirine at the recommended dosing levels

2.2 Secondary Objectives

- To assess the best response on study treatment (Part A only)
- To assess the duration of response (Part A only)
- To assess overall survival (OS)

2.3 Additional Objectives

- To assess the pharmacokinetics, antitherapeutic antibodies (ATA), and pharmacodynamics of vadastuximab talirine
- To assess event-free survival (EFS)
- To assess the rate of MRD negativity
- To assess lymphocyte subset recovery after alloSCT
- To assess CD33 expression levels and post-treatment target (CD33) saturation
- To assess biomarkers of biological activity, resistance, and treatment outcome

2.4 Endpoints

2.4.1 Safety Endpoints

- Type, incidence, severity, seriousness, and relatedness of adverse events (AEs)
- Type, incidence, and severity of laboratory abnormalities
- Incidence of dose-limiting toxicity (DLT)

2.4.2 Efficacy Endpoints

- One-year survival
- Day –1 and Day 30 rates of MRD negativity (Part A only)
- Complete remission rate (Part A only)
- Best response (Part A only)
- Duration of response (Part A only)
- Overall survival

2.4.3 Additional Endpoints

- MRD – negativity
- Event-free survival
- PK parameters for SGN-CD33A, and released SGD-1882
- Incidence of ATA
- Biomarkers of vadastuximab talirine activity
- Quantification of T-, B-, and NK-cell lymphocyte subsets post-transplant

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design (Parts A and B)

This is a phase 1/2, open-label study designed to evaluate the safety and efficacy of vadastuximab talirine in patients with relapsed chemo-resistant AML, for cytoreduction pre-conditioning and post-alloSCT maintenance. The study will consist of phase 1 (safety) followed by phase 2 (expansion) in each part of the study. Parts A and B will enroll concurrently. Phase 2 will be initiated following dose level recommendation by the SMC with the determination of the MTD or recommended phase 2 doses for Parts A and B, and an evaluation of safety.

At the discretion of the SMC, dose levels may be expanded in up to 12 patients in the phase 1 portion of Parts A and B.

An SMC consisting of the study medical monitor, investigators, and the study biostatistician will monitor the safety of patients treated with vadastuximab talirine on a regular basis throughout the study, including reviews of the data pertinent to dose-escalation decisions. Reviews of the aggregate safety data will be routinely initiated to evaluate any emerging safety signals with respect to cumulative toxicity. The SMC may recommend investigation of an intermediate dose level during dose escalation. Dose levels for expansion will be selected by the SMC based on known safety and activity data.

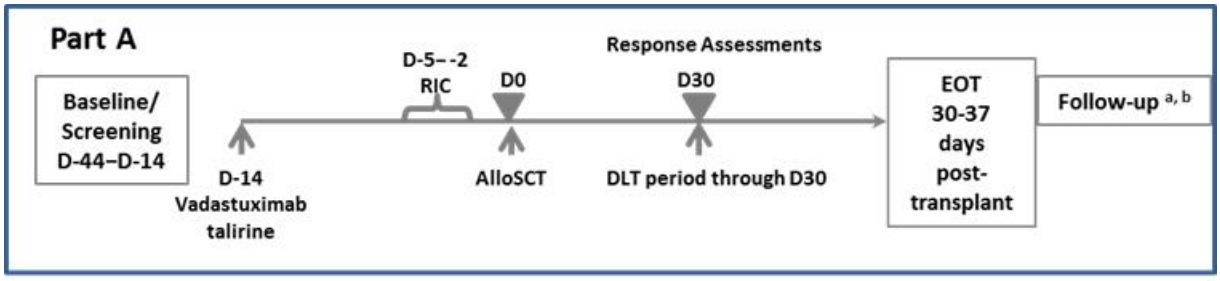
All patients will be followed for survival status until 5 years after the last patient is enrolled, or until study closure, whichever occurs first.

3.1.1 Part A – Pre-AlloSCT

One dose of vadastuximab talirine will be administered intravenously on Day −14 followed by reduced intensity chemotherapy (RIC) of melphalan and fludarabine on Days −5 to −2. Study days are relative to the day of alloSCT, which occurs on Day 0.

Patients will be evaluated for response at Day 30 and every 3 months from transplant for 1 year and then every 6 months until 3 years post-transplant (no longer required once disease progression is documented). A schematic for Part A is presented below.

Figure 1: Part A Design



a Response assessments every 3 months (±2 weeks) from transplant for the 1st year and then every 6 months (±2 weeks) until 3 years post-transplant (no longer required once disease progression is documented).

b Long-term follow-up (consisting of a phone call for survival and collection of subsequent therapy information when a clinic visit is not required) will occur every month (±1 week) from transplant for the first 2 years, and then every 3 months (±2 weeks) until death or study closure.

Part A phase 1 of the study will be conducted using a standard 3+3 design starting at Dose Level 1. Cohorts of 3 patients will be enrolled into each new cohort. If 0 of 3 patients experience a DLT (defined in Section 3.1.1.1), the next dose level will be opened to enrollment. If ≥2 of 3 patients in a cohort experience a DLT, the MTD will have been exceeded and dose escalation will stop. If 1 of 3 patients in a cohort experiences a DLT, an additional 3 patients will be treated at that same dose level for a total of 6 patients. If none of the 3 additional patients experiences a DLT (1 of 6 patients with a DLT), dose escalation will continue to the next higher dose level. If 1 or more of the 3 additional patients experiences a DLT (≥2 of 6 patients with a DLT), the MTD will have been exceeded and dose escalation will not continue. Patients who do not complete the DLT-evaluation period due to non-DLT reasons will be replaced. Dose de-escalation from Dose Level 1 is permitted based on SMC recommendation; the planned doses for Part A are summarized in Table 1.

Table 1: Part A dose levels

Dose Level for Part A	Part A Dose of Vadastuximab Talirine (mcg/kg)
−1	30
1	40
2	60
3	80
4	100

Part A phase 2 will explore the activity and safety of vadastuximab talirine in 36 patients at a dose level, not to exceed MTD, recommended by the SMC. An additional 36 patients may be enrolled in Part A phase 2 at a dose level also recommended by the SMC for further characterization of the safety and efficacy profile of vadastuximab talirine.

3.1.1.1 Dose-Limiting Toxicity – Part A

The DLT-evaluation period is from the time of vadastuximab talirine administration through 30 days post-alloSCT. DLTs in Part A will be defined as the following:

- Failure to achieve a sustained absolute neutrophil count of 500 by Day 30 (defined as the first of 3 consecutive days with an ANC of ≥500) in the absence of leukemia, infection, or acute graft-versus-host disease (GVHD).
- Any Grade 3 toxicity within 30 days post-alloSCT according to the Bearman Toxicity Criteria (Bearman 1988) (see Appendix E).
- The SMC will review any clinically significant non-hematologic AE ≥ Grade 3 that is considered related to vadastuximab talirine and/or vadastuximab talirine + fludarabine/melphalan conditioning, and is not attributed to chemotherapy alone, for consideration as a DLT. Adverse events will be assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.03.

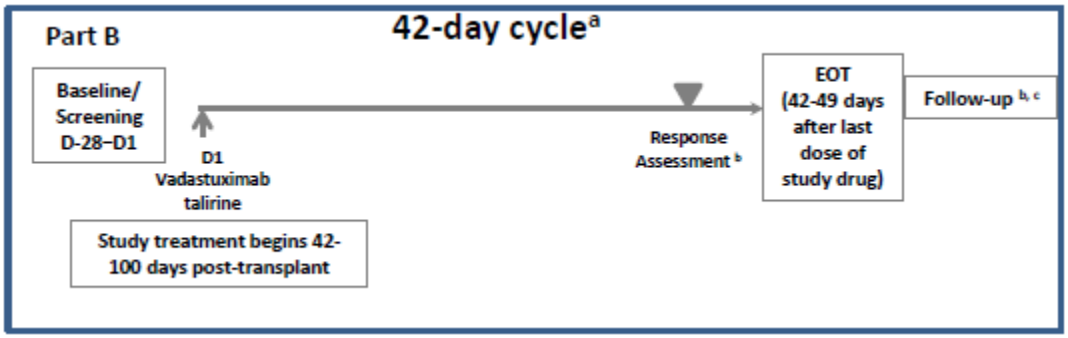
3.1.2 Part B – Post-AlloSCT

Patients in Part B of the study will begin treatment between 42 and 100 days post-alloSCT and will receive vadastuximab talirine on Day 1 of 42-day cycles for up to 8 cycles. Study days are relative to the first dose of vadastuximab talirine, which occurs on Day 1. Patients who receive clinical benefit may continue treatment for an additional 8 cycles (up to a total of 16 cycles) with medical monitor approval.

Response assessments will be every 3 months after the first dose of study drug for 2 years (every other cycle during treatment), and then every 6 months until 3 years post-transplant. Patients in Part B who discontinue study treatment prior to relapse will be evaluated for response until progression or initiation of new anticancer treatment, whichever comes first.

The study scheme is presented as follows:

Figure 2: Part B Design



a For up to 12 months
b Every 3 months (±2 weeks) for 2 years after dosing and every 6 months (±2 weeks) until 3 years post-transplant. No are longer required after documentation of disease progression.
c Long-term follow-up (consisting of a phone call for survival and collection of subsequent therapy information when a clinic visit is not required) will occur every 1 month (±1 week) for the first 2 years after receiving the first dose of study treatment, and then every 3 months (±2 weeks) until death or study closure.

The planned doses for Part B are summarized in Table 2.

Table 2: Part B dose levels

Dose Level for Part B	Part B Dose of Vadastuximab Talirine (mcg/kg)
–1	5
1	10

Six patients will be treated at Dose Level 1 beginning between 42 and 100 days post-transplant. Once these 6 patients have completed the DLT period, the sponsor, in consultation with the SMC, may decide to explore safety and activity in an additional 6 patients. In the event of DLT (as defined below in Section 3.1.2.1) occurring in 2 or more patients in either the first or the second 6-patient cohort, the sponsor, in consultation with the SMC, may choose to modify the schedule or dose level for further investigation. If fewer than 2 DLTs occur in either the first or second 6-patient cohorts, the sponsor will determine, in consultation with the SMC, the day when therapy may start and the recommended dose for further evaluation.

Part B phase 2 will explore the activity and safety of vadastuximab talirine in 36 patients at a dose level recommended by the SMC.

3.1.2.1 Dose-Limiting Toxicity – Part B

The DLT-evaluation period is the first cycle of treatment. DLT will be defined as the following:

- Any hematologic toxicity that delays the start of the second cycle more than 1 week will be considered a DLT.
- The SMC will review any clinically significant non-hematologic AE ≥ Grade 3 that is considered related to vadastuximab talirine for consideration as a DLT. Adverse events will be assessed according to the NCI CTCAE version 4.03.

3.1.3 Study Stopping Criteria

[redacted]

3.1.3.1 Rationale for stopping criteria

For AML patients in first remission, non-relapse mortality rates at 100 days post-transplant have ranged from 6% to 20%, many of which are caused by treatment-related toxicity, (Schmid 2005; Lim 2015). In contrast, the reported 100 day non-relapse mortality rates in patients who are not in CR at time of transplant ranges from 25%–62% (Wong 2005; Lim 2015; Hamadani 2016), although limited data exist. Patients undergoing transplantation with active leukemia often have persistent cytopenias and are at higher risk for non-relapse mortality compared to patients transplanted in remission primarily due to their inability to recovery from the toxicities of prior chemotherapy (mucositis/colitis) and complications of prolonged bone marrow suppression. Given these considerations and as a conservative approach, an on-study toxic-death rate in excess of 20% at 100 days post-transplant is considered grounds to halt this study.

The incidence of SOS or VOD of the liver has been reported to range from 11%–40% in AML patients undergoing allogeneic stem cell transplantation (Dalle 2016). Severe SOS/VOD, defined by Carreras et al. as death directly attributable to SOS/VOD or SOS/VOD not resolved on or after Day 100, occurs in approximately 40% of patients who develop SOS/VOD after receiving allogeneic transplant for malignancies or bone marrow failure syndromes (Carreras 2011). Several risk factors have been reported to be associated with the development of SOS/VOD, such as the presence of advanced disease, a high red cell transfusion burden, and use of fludarabine in the transplant conditioning regimen, all of which can be commonly seen in our expected treated population. Although fludarabine and melphalan (Flu/Mel) are conventionally considered a RIC regimen, the myelosuppressive nature of vadastuximab talirine compounds the effects of Flu/Mel thereby increasing the overall intensity of the regimen. In the phase 1 first in human study SGN33A-001, doses of 50 mcg/kg or higher of vadastuximab talirine induced significant bone marrow suppression when used to treat patients with relapsed/refractory AML (Stein 2015). Therefore, the intensity of Flu/Mel/vadastuximab talirine should be considered closer to standard myeloablative conditioning rather than reduced intensity conditioning. Based upon the

totality of historical data and the aforementioned considerations, severe SOS/VOD occurring in greater than 10% of treated patients would be unacceptable compared to the anticipated rate.

Acute GVHD (aGVHD) involving the liver, (either single or multi-organ) has been reported in 16% of patients receiving tacrolimus/methotrexate GVHD prophylaxis (Yagasaki 2009). Additionally, patients undergoing transplant with active AML are at increased risk for hepatic aGVHD of any grade, particularly with a trend suggesting increased the risk of developing Grade 3 or 4 aGVHD (Arai 2016; Araki 2016). Therefore, Stage 3 liver GVHD rate of 20% is an appropriate stopping criterion for this study.

Failure of engraftment has been reported to occur in 5%–10% of patients undergoing transplantation for AML (Blaise 2007). Based on historical rates, graft failure is anticipated to occur in 10% of patients transplanted for relapsed/refractory AML (Duval 2010). Patients in this trial who undergo transplantation with heavily treated but still active disease are likely to be at higher risk of graft failure due to the additive effects of bone marrow infiltration by active leukemia and dysfunction secondary to previous treatment with intensive chemotherapy. Thus, a graft failure rate of more than 10% is above the expected rate and a reasonable stopping criterion for this study.

3.2 Discussion and Rationale for Study Design

The initial phase 1 portion of this study will evaluate the safety and tolerability of escalating doses of vadastuximab talirine administered as pre-cytoreduction prior to an alloSCT for patients with relapsed and/or refractory AML. The study will also assess the safety and tolerability of low doses of vadastuximab talirine post-transplant in relapsed/refractory patients who have achieved a complete remission following a transplant performed in the setting of active disease. Because there is limited experience with the use of vadastuximab talirine in the peri-transplant setting, the cohorts will be assessed independently to determine the safety and tolerability of vadastuximab talirine as a single high-dose infusion pre-transplant and as repeated low-dose therapy in the post-transplant setting.

In the Phase 2 portion of the study, the leukemia effect of vadastuximab talirine will also be assessed independently in both cohorts of patients and the data acquired in this study will provide further information to guide the development of this agent in the treatment of AML.

3.2.1 Method of Assigning Patients to Treatment Groups

Parts A and B will enroll concurrently. Patients cannot be enrolled to both Part A and Part B.

3.2.2 Rationale for Selection of Doses

A first in human phase 1 dose escalation study of vadastuximab talirine (SGN33A-001) administered IV every 3 weeks for no more than 4 cycles in patients with CD33-positive AML evaluated doses ranging from 5 to 60 mcg/kg. For patients achieving a response (CR or CRi) vadastuximab talirine was administered at doses of 5 and 10 mcg/kg every 3 to 6 weeks until disease recurrence or unacceptable toxicity. In patients with active disease at

doses ≥50 mcg/kg, significant bone marrow suppression was observed resulting in prolonged pancytopenia. It is postulated that in the setting of an alloSCT, doses >40 mcg/kg may be tolerable without incurring prolonged cytopenias due to engraftment of normal stem cells leading to timely restoration of hematopoiesis. Therefore the starting dose for the pre-transplant part of the study is 40 mcg/kg as a single infusion in combination with a reduced intensity conditioning regimen. For patients in Part B who have undergone an alloSCT for active disease and have achieved a CR or CRi the starting dose of the trial will be 10 mcg/kg administered every 6 weeks, a dose that has been well tolerated in patients treated on the initial phase 1 trial of vadastuximab talirine.

3.2.3 Blinding

This is a phase 1/2, open-label study.

4 STUDY POPULATION

Patients must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of Good Clinical Practice (GCP) audit and/or health regulatory authority inspection.

4.1 Inclusion Criteria

1. Relapsed/refractory acute myeloid leukemia (AML), with the exception of acute promyelocytic leukemia (APL).

   - The following part-specific criteria:

For Part A

- Relapsed/refractory AML (>5% blasts)
  - Patients who have received 2 or 3 previous induction regimens including at least one intensive chemotherapy regimen. Patients who receive 2 cycles of therapy as part of their initial AML remission induction therapy will be considered as having undergone one induction regimen.
  - Patients are eligible after only 1 previous induction regimen if one of the following apply:
    - Age ≥60 years (but ≤75 years)
    - First complete remission (CR) duration <6 months
    - Adverse karyotype per Medical Research Council classification (Grimwade 2001)
    - Secondary AML (prior history of MDS or therapy-related)
    - FLT3-ITD mutation

- Availability of an HLA matched related or unrelated donor.
- Eligible for an alloSCT according to institutional guidelines.

For Part B

- Transplant (no donor type excluded) must have been performed with active AML (>5% blasts) using a conventional conditioning regimen and have achieved CR or CRi post-alloSCT (with ANC ≥1,000 and platelet ≥50,000 and platelet transfusion independent x1wk prior to dosing). Documentation of CR or CRi is required within 14 days of first dose of study treatment.
- Treatment must begin at least 42 days, but no more than 100 days post-transplant.

2. An Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (see Appendix C).
3. Age ≥18 and ≤75 years.
4. The following baseline laboratory data:
   - Serum total bilirubin ≤2x upper limit of normal (ULN) or ≤3x ULN for patients with Gilbert's disease.
   - Serum creatinine ≤2x ULN and calculated creatinine clearance ≥60 mL/min.
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3x ULN.
5. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test result within 7 days prior to the first dose of vadastuximab talirine and must agree to use two effective contraception methods during the study and for 6 months following the last dose of study drug. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.
6. Males who have partners of childbearing potential must agree to use two effective contraceptive methods during the study and for 6 months following the last dose of study drug.
7. Patients must provide written informed consent.
8. Left ventricular ejection fraction at rest ≥45%.
9. Diffusing capacity of the lungs for carbon monoxide (DLCO; corrected for hemoglobin), forced expiratory volume in 1 second (FEV1), and forced vital capacity (FVC) greater than 50% of predicted

4.2 Exclusion Criteria

1. Central nervous system leukemia strongly suspected based on altered neurologic status or documented by positive cytology in cerebral spinal fluid. Intrathecal CNS prophylaxis is allowed.
2. Patients may not have received vadastuximab talirine previously.

3. Any uncontrolled Grade 3 or higher (per NCI CTCAE, Version 4.03) viral, bacterial, or fungal infection ongoing prior to the first dose of any component of study treatment. Antimicrobial prophylaxis or ongoing treatment of resolving/controlled infection is permitted.
4. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association Class III-IV within 6 months prior to the first dose of any component of study treatment (see Appendix D).
5. Any known history of Hepatitis B (HBSAg positive), Hepatitis C, or HIV.
6. Current therapy (defined as within 14 days prior to first dose of vadastuximab talirine) with other systemic antineoplastic, immunosuppressive (except for GVHD treatment/prophylaxis in Part B), or investigational agents, other than as described in Section 5.10.2, Allowed Concomitant Therapy. For Part A, hydroxyurea or 6-mercaptopurine used for cytoreduction may be given up to 1 day prior to treatment.
7. Known hypersensitivity to excipients contained in the drug formulations of vadastuximab talirine, fludarabine, melphalan, tacrolimus, or methotrexate.
8. Females who are breastfeeding.
9. Any of the following:
    - History of another primary invasive malignancy that has not been in remission for at least 3 years. The following are exempt from the 3-year limit: curatively treated non-melanoma skin cancer; curatively treated, localized prostate cancer; and low grade prostate cancer suitable for active surveillance; locally treated, localized cervical cancer.
    - Any history of metastatic malignancy.
10. For Part A
    - Partially matched related and unrelated donors, cord blood cells are excluded as the source of hematopoietic stem cells.
    - Prior alloSCT
11. For Part B
    - Active GVHD Grade 2 or higher
    - History of Grade 2 or higher hepatic GVHD
    - Concurrent use of corticosteroids equivalent of prednisone at a dose of >0.5 mg/kg
    - History of veno-occlusive disease (VOD) requiring defibrotide

4.3 Removal of Patients from Therapy or Assessment

Seattle Genetics or their designee must be notified if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records and case report form (CRF).

4.3.1 Discontinuation of Study Drug

A patient's treatment with study drug may be discontinued for any of the following reasons:

- Completed treatment
- Leukemic relapse/progression
- Adverse event (AE)
- Investigator decision
- Patient decision, Non-AE
- Study termination by sponsor
- Other, Non-AE

4.3.2 Patient Withdrawal from Study

Any patient may be discontinued from the study for any of the following reasons:

- Completed study per protocol
- Patient withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

5 TREATMENTS

5.1 Treatments Administered

Vadastuximab talirine (SGN-CD33A) will be administered IV push without routine premedication.

- Part A: administered on Day –14 (dose levels starting at 40 mcg/kg; see Table 1)
- Part B: administered on Day 1 of 42-day cycles at either 5 or 10 mcg/kg; see Table 2

Part A only – (pre-allo SCT)

Reduced Intensity Conditioning Regimen

- Fludarabine 30 mg/m^2/day IV on Day –5 to Day –2 (total dose of 120 mg/m^2)
- Melphalan 140 mg/m^2 IV on Day –2

GVHD prophylaxis

- Tacrolimus 0.03 mg/kg/day IV/PO (initial dose Day –1 strongly preferred; starting day may follow institutional practice if approved by the study medical monitor); subsequent doses IV or oral target blood trough levels 5–15 ng/mL.
- Methotrexate 5–10 mg/m^2 IV on Day 1 and 5 mg/m^2 IV on Days 3, 6, and 11 post-transplant

5.2 Investigational Study Drug

Detailed information describing the preparation, administration, and storage of vadastuximab talirine (SGN-CD33A) is located in the Pharmacy Binder.

5.2.1 Description

Vadastuximab talirine is a sterile, preservative-free, lyophilized cake or powder for reconstitution for IV administration. Vadastuximab talirine is supplied by Seattle Genetics in single-use amber glass vials. Drug product vial contains vadastuximab talirine, [redacted] Drug product vials are labeled with a nominal content of 5 mg/vial. Each vial contains 6 mg of vadastuximab talirine to ensure the labeled quantity (5 mg/vial) may be withdrawn for use.

5.2.2 Dose and Administration

Dosing is based on patient actual body weight (to the nearest tenth of a kilogram) assessed within 3 days of each cycle. An exception to weight-based dosing is made for patients weighing greater than 100 kg; doses will be based on 100 kg for these individuals.

Administration of vadastuximab talirine will be performed via IV push. It is recommended that vadastuximab talirine is administered via central venous access port (e.g., peripherally inserted central catheter [PICC], Hickman line, or similar according to institutional standard). However, if SGN-CD33A is not administered via central venous access port, a secure and free-flowing peripheral line must be used. Follow institutional guidelines for the administration of chemotherapy and take precautions to prevent extravasation per institutional standards and as described in "Preventing and Managing Vesicant Chemotherapy Extravasations" (Schulmeister 2010).

A sterile 0.2 µm filter must be used in the administration of SGN-CD33A. After the infusion, the IV infusion line (including the filter and any associated tubing or closed-delivery injection devices) must be flushed with at least 20 mL of saline. See the Pharmacy Binder for details.

5.2.3 Fludarabine/Melphalan/Tacrolimus/Methotrexate

Fludarabine

Fludarabine alone and in combination with other anticancer agents is indicated for the treatment of various lymphoproliferative disorders including chronic lymphocytic leukemia and indolent non-Hodgkin lymphomas. Because of its immunosuppressive effects it is also used in conditioning regimens prior to an alloSCT. Fludarabine for intravenous injection

contains a sterile lyophilized fludarabine cake which is freely soluble in water. Fludarabine is a fluorinated nucleotide analog that is relatively resistant to deamination by adenosine deaminase.

Melphalan

Melphalan alone and in combination is indicated in the treatment of multiple malignancies including multiple myeloma, ovarian and breast cancer. Because of its myelosuppressive properties it is also used in conditioning regimens prior to allogeneic and autologous stem cell transplant. Melphalan for injection contains a sterile nonpyrogenic freeze-dried powder which is reconstituted with a sterile diluent containing sodium citrate, propylene glycol, ethanol and water. Melphalan is a bifunctional alkylating agent which enables covalent binding to DNA, cross-linking two DNA strands thereby preventing cell replication.

Tacrolimus

Tacrolimus is an immunosuppressive agent that is indicated for prevention of graft rejection in patients undergoing solid organ transplantation. It is also used routinely for the prevention of GVHD in patients undergoing allogeneic hematopoietic stem cell transplantation. Tacrolimus, available in both oral (0.5, 1 and 5 mg capsules) and IV (crystalline powder freely soluble in methanol and chloroform) formulations is a calcineurin inhibitor which blocks T-lymphocyte activation.

Methotrexate

Methotrexate is indicated for the treatment of various malignancies as well as autoimmune disorders. It is also commonly used as part of an immunosuppressive regimen for the prevention of GVHD in patients undergoing allogeneic hematopoietic stem cell transplantation. Methotrexate for injection is available as a lyophilized powder that is reconstituted with sterile water. It competitively inhibits dihydrofolate reductase resulting in the reduction of folic acid production which is essential for DNA, RNA, and protein synthesis.

5.3 Management of Infusion Reactions

Infusion-related reactions may occur during the infusion of vadastuximab talirine. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include administering medications for infusion-related reactions.

Patients who have experienced an infusion-related reaction may be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid administered 30–60 minutes prior to each infusion or according to institutional standards. Should a patient experience infusion-related reactions in the setting of premedication, continued treatment with SGN-CD33A must be discussed with the medical monitor prior to the next planned dose.

If anaphylaxis occurs, study treatment administration should be immediately and permanently discontinued.

5.4 Management of Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) prophylaxis is strongly recommended in patients with measurable AML. Hydration and effective urine flow rates remain a cornerstone of TLS prevention and treatment and should be employed as per institutional standards, in addition to medications to prevent or treat hyperuricemia (e.g., allopurinol, rasburicase).

Patients must be monitored for TLS according to the institutional standard. Recommended monitoring measures include frequent assessment of electrolyte levels and cardiac function for the first 48–72 hours following study drug administration. Additionally, it is recommended that patients are monitored for signs and symptoms of fluid volume overload, such as peripheral edema, neck vein distension, weight gain, and pulmonary crackles, as well as signs and symptoms of fluid volume deficit, such as dry mucous membranes, poor skin turgor, weight loss, and thirst. The use of physical assessment, strict intake and output, daily weights, and lab work results to monitor renal function are recommended measures to monitor for TLS.

In the event of TLS, immediate treatment must be administered according to the institutional standard, including hydration, administration of xanthine oxidase inhibitors or recombinant uricase, supportive care for electrolyte disturbances, and hemodialysis or hemofiltration if required.

5.5 Dose Modifications for Part B

Patients who experience events that meet the criteria for DLT (defined in Section 3.1.2.1) at any time in the study must permanently discontinue vadastuximab talirine, unless the investigator and medical monitor agree that the patient may receive a lower dose of vadastuximab talirine.

After the DLT evaluation period, treatment delays are permitted for hematological adverse events at the discretion of the investigator to allow for recovery of platelets and neutrophils. If toxicity is not recovered within 42 days after prior cycle, consideration can be given to either resume with dose reduction by one level, or discontinue vadastuximab talirine.

Additional dose modifications for toxicity are applicable for Cycle 2 and beyond of Part B. These modifications are presented in Table 3. The dose modifications provided below should serve as guidance; alternative approaches may be discussed with the medical monitor.

Individual dose decreases are permitted at the discretion of the medical monitor and site investigator. Intrapatient dose escalation is not permitted. Cycles may only be administered with a platelet count of ≥50,000 and an ANC of ≥1000.

Table 3: Recommended dose modifications for vadastuximab talirine-associated non-hematological toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at same level	Continue at same level	Withhold dose until toxicity is ≤ Grade 2 or baseline, then resume treatment at the same dose level[a,b]	Withhold dose until toxicity is ≤ Grade 2 or baseline, then resume treatment, or discontinue at the discretion of the investigator[a]

a Patients with Grade 3 or 4 electrolyte abnormalities may continue study treatment without interruption.
b Treatment should be discontinued for patients who experience Grade 3 infusion-related reactions, unless otherwise discussed with medical monitor. For a second occurrence, reduce by one dose level.

If vadastuximab talirine is permanently discontinued, patients will be considered off study treatment.

5.6 Storage and Handling

Single-use amber vials containing vadastuximab talirine must be stored under refrigeration at 2 to 8°C, protected from light (both sunlight and artificial light), in an appropriate locked room accessible only to the pharmacist, investigator, or a duly designated person.

Chemical and physical stability of the reconstituted drug product has been demonstrated for 24 hours at 2 to 8°C, protected from light. However, vadastuximab talirine drug product does not contain preservatives; therefore, from a microbiological standpoint, opened and reconstituted vials should be used immediately. If not used immediately, the in-use storage of the reconstituted product should not be longer than 24 hours under refrigeration at 2 to 8°C. If dilution is needed, the reconstituted drug product should be diluted in 0.9% Sodium Chloride Injection, USP, at the time of use. The prepared dosing solution (reconstituted drug product or drug product dilution) may be kept for up to 4 hours at room temperature in the amber vial.

It is recommended that the drug product vials and solutions be protected from light (both sunlight and artificial light) until the time of use.

Do not shake reconstituted or diluted vadastuximab talirine.

Any partially used vials or prepared dosing solutions should be discarded by the site according to institutional drug disposal procedures. Unused vials should not be discarded by the site prior to authorization by the Sponsor.

Drug accountability instructions are provided in the Pharmacy Binder.

Refer to Section 5.2.3 and the fludarabine, melphalan, tacrolimus, and methotrexate package inserts for appropriate storage and handling instructions.

5.7 Packaging and Labeling

Vadastuximab talirine is supplied in an amber glass vial to protect from light. The drug product vials are labeled as SGN-CD33A for injection (h2H12ec-SGD-1910) 5 mg/vial.

Refer to Section 5.2.3 and the fludarabine, melphalan, tacrolimus, and methotrexate package inserts for packaging and labeling information.

5.8 Preparation

Recommended safety measures for handling and preparation include masks, protective clothing, gloves (double glove with nitrile gloves), and vertical laminar airflow safety cabinets.

Before administration, vadastuximab talirine must be reconstituted. The reconstituted drug product may be further diluted depending on the dose level. Diluted solutions of vadastuximab talirine are stable at concentrations ≥0.6 mg/mL and ≤3 mg/mL. The formulation contains no preservative and is intended for single use only; solutions should be prepared and transferred using aseptic technique in a biosafety hood.

Detailed drug preparation instructions are provided in the Pharmacy Binder.

Preparation of fludarabine, melphalan, tacrolimus and methotrexate should be according to the appropriate package insert and in adherence to institutional standards.

5.9 Required Premedication and Postmedication

None.

5.10 Concomitant Therapy

All concomitant medications and blood products administered will be recorded from time of first dose of vadastuximab talirine administration through the safety reporting period. Any concomitant medication given for a study protocol-related adverse event should be recorded from the time of informed consent.

5.10.1 Required Concomitant Therapy

None.

5.10.2 Allowed Concomitant Therapy

Routine premedication for infusion reactions should not be administered prior to the first dose of vadastuximab talirine. However, patients who experience an infusion-related reaction (with the exception of anaphylaxis) may receive subsequent treatment with premedication as described in Section 5.3.

Donor lymphocyte infusion (DLI) or stem cell boost can be used to treat decreasing engraftment.

Defibrotide is permitted for the treatment of VOD

For Part B, immunosuppressive agents are allowed for prophylaxis against and treatment of GVHD.

Antimicrobial prophylaxis measures are strongly recommended, per institutional standard of care. Antiemetics should be used per institutional standard.

Prophylactic treatment/measures are strongly recommended for patients at risk for TLS, per the institutional standard [e.g., treatment with allopurinol or rasburicase, as well as adequate hydration (Coiffier 2008)].

The use of red blood cell (RBC) and platelet transfusions, and/or colony-stimulating factors per institutional practice is permitted. Intrathecal prophylactic treatment for patients at risk for cerebral/meningeal disease is permitted at the discretion of the investigator.

5.10.3 Prohibited Concomitant Therapy

Patients may not receive other investigational drugs, radiotherapy, or systemic antineoplastic therapy prior to the end of the treatment visit.

DLI is not permitted as a treatment for a loss of MRD negativity or a loss of molecular response.

Treatment with sirolimus is not permitted in Part A.

5.11 Treatment Compliance

Study drug administration will be performed by study site staff and documented in source documents and the CRF.

6 STUDY ACTIVITIES

Adverse events and concomitant medications will be recorded from Day –14 for Part A (Pre-alloSCT) and from Day 1 for Part B (Post-alloSCT) through the safety reporting period (see Section 7.6.2.3). Any study protocol-related adverse event should be recorded from the time of informed consent as well as any concomitant medications given for treatment of the adverse event. A schedule of events is provided in Appendix A for Part A and in Appendix B for Part B. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

6.1 Part A – pre-AlloSCT (Days relative to transplant Day 0)

6.1.1 Screening Period (Days –44 to –14)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history
- Procedures to assess transplant eligibility (does not need to be repeated if performed within 42 days of enrollment):
  - Urine creatinine clearance

- Spot urine for protein and creatinine
- HCT-specific comorbidity index. The HCT Comorbidity Index Calculator, www.hctci.org/Home/Calculator. Accessed August 25, 2015.
- ECHO/MUGA
- DLCO and FEV1
- CMV antibody test, hepatitis panel (Hep A Ab, HepB Sab, HepB Sag, HepB Core Ab, HepC Ab), herpes simplex, HIV and HTLV1 I/II antibody and varicella zoster virus

6.1.2 Day –28 to Day –14

- Bone marrow examination
- Biomarker sample collection (see Table 4 and Table 5)

6.1.3 Day –21 to Day –14

- Physical exam with weight
- Serum chemistry panel
- Complete blood count (CBC) with differential
- ECOG performance status
- β-hCG pregnancy test for females of childbearing potential

6.1.4 Day –14

- Physical exam with weight (not required if conducted within prior 24 hours)
- Serum chemistry panel (not required if conducted within prior 24 hours)
- CBC with differential (not required if conducted within prior 24 hours)
- Vadastuximab talirine administration
- ECOG performance status
- Blood samples for PK, ATA, and biomarkers (see Table 4)

6.1.5 Day –13

- Blood samples for PK (see Table 4)

6.1.6 Day –11

- Blood samples for PK and biomarkers (see Table 4)

6.1.7 Day –7

- Serum chemistry panel
- CBC with differential
- Spot urine for protein and creatinine
- Blood samples for PK and biomarkers (see Table 4)

6.1.8 Day –5 to –2

- Fludarabine 30 mg/m^2/day IV on Day –5 to Day –2 (total dose of 120 mg/m^2)

- Melphalan 140 mg/m^2 IV on Day –2

6.1.9 Day –1

- Bone marrow aspirate for MRD and PK (see Table 5)
- Blood samples for PK, ATA, and biomarkers (see Table 4)
- Start tacrolimus 0.03 mg/kg/day IV (subsequent oral or IV doses target blood trough levels 5–15 ng/mL)

6.1.10 Day 0

- Serum chemistry panel
- CBC with differential
- AlloSCT

6.1.11 Day 1

- Methotrexate 5–10 mg/m^2 (and subsequent doses at 5 mg/m^2 IV on Days 3, 6, and 11 post-transplant).

6.1.12 Days 7, 14, and 21

- Serum chemistry panel
- CBC with differential

6.1.13 Day 30 (±2 days)

- Serum chemistry panel
- CBC with differential
- Blood samples for biomarkers (see Table 4)
- Spot urine for protein and creatinine
- BM aspirate for MRD and biomarkers (see Table 5)
- BM examination for response assessment
- Chimerism assay per institutional guidelines and schedule
- GVHD assessments

6.1.14 End of Treatment Visit (30 to 37 days post-transplant)

End of Treatment (EOT) visits should occur 30 to 37 days post-transplant. However, EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 30 days post-transplant, the patient will be contacted 30 to 37 days following transplant to assess for adverse events.

- Physical exam (does not need to be repeated if done within 7 days prior)
- Serum chemistry panel (does not need to be repeated if done within 7 days prior)
- CBC with differential (does not need to be repeated if done within 7 days prior)
- Pregnancy test
- ECOG performance status

6.1.15 Long-Term Follow-Up

In the absence of disease progression, the following assessments should be obtained every 3 months (±2 weeks) from transplant for the first year and then every 6 months (±2 weeks) until 3 years post-transplant:

- If a response assessment is conducted per site standard, sites should report the assessment results to the sponsor
- GVHD assessment, if conducted per site standard

The above assessments are no longer required once disease progression is documented.

Long-term follow-up (consisting of a phone call for survival and collection of subsequent therapy information when a clinic visit is not required) will occur every month (±1 week) from transplant for the first 2 years, and then every 3 months (±2 weeks) until death or study closure. Events of SOS/VOD that occur within 180 days of the last dose of vadastuximab talirine will be reported to the sponsor, regardless of causality. Patients who undergo subsequent allo-SCT within 180 days of the last dose of vadastuximab talirine in the absence of relapse and additional therapy will be followed for SOS/VOD for 100 days post-transplant (Section 7.6.2.4 Adverse Events of Special Interest).

6.2 Part B – post alloSCT (Days relative to the first dose of vadastuximab talirine on Day 1)

6.2.1 Screening Visit (Days –28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history
- GVHD assessments

6.2.2 Baseline Visit (Day –14 to 1)

- BM examination
- Bone marrow aspirate for MRD
- Biomarker sample collection (see Table 6)

6.2.3 Day –7 to 1

- Physical exam with weight
- β-hCG pregnancy test for females of childbearing potential
- ECOG performance status
- Serum chemistry panel
- CBC with differential
- Spot urine for protein and creatinine

6.2.4 Day 1

- Physical exam with weight (not required if conducted within prior 24 hours)
- Serum chemistry panel (not required if conducted within prior 24 hours)
- CBC with differential (not required if conducted within prior 24 hours)
- Vadastuximab talirine administration
- Blood samples for PK, ATA, and biomarker assessments (see Table 6) (on Day 1 of Cycles 1, 2, 3, 5 and 7)
- Bone marrow aspirate for MRD and biomarker assessments (Day 1 of Cycle 3 and every 2 cycles while on treatment)
- GVHD assessments (on Day 1 of all cycles)
- Bone marrow examination (Day 1 of Cycle 3 and every 2 cycles while on treatment)

6.2.5 Day 2 (Cycle 1 only)

- Blood samples for PK (see Table 6)

6.2.6 Day 4 (Cycle 1 only)

- Blood samples for PK (see Table 6)

6.2.7 Day 8, 15, 22, and 28 (Cycle 1 only, ±1 day)

- Serum chemistry panel
- CBC with differential

6.2.8 Day 42 (Cycle 1 only)

The following assessments are not required if ANC recovers ≥1000 and platelets recover to ≥50,000:

- Serum chemistry panel
- CBC with differential

6.2.9 End of Treatment Visit (42 to 49 days after last dose of study drug)

If any of the following evaluations have already been performed, they do not need to be repeated. If any of the following samples have not been obtained, collection is not required (Amendment 3).

End of Treatment (EOT) visits should occur 42 to 49 days following the last dose of study drug. However, EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 42 days after the last study treatment, the patient will be contacted 42 to 49 days following the last treatment to assess for AEs.

- Serum chemistry panel
- CBC with differential
- Spot urine for protein and creatinine
- Blood samples for PK, ATA, and biomarker assessments (see Table 6)

- Bone marrow aspirate for MRD and biomarker assessments (see Table 6)
- BM examination (if not performed within 42 days prior)
- Pregnancy test
- GVHD assessments
- ECOG performance status

6.2.10 Long-Term Follow-up

In the absence of disease progression, the following assessments should be obtained every 3 months (±2 weeks) for the first 2 years after receiving the first dose of study treatment and then every 6 months (±2 weeks) until 3 years post-transplant.

- If a response assessment is conducted per site standard, sites should report the assessment results to the sponsor
- GVHD assessment, if conducted per site standard

The above assessments are no longer required once disease progression is documented.

Long-term follow-up (consisting of a phone call for survival and collection of subsequent therapy information when a clinic visit is not required) will occur every 1 month (±1 week) for the first 2 years after receiving the first dose of study treatment, and then every 3 months (±2 weeks) until death or study closure. Events of SOS/VOD that occur within 180 days of the last dose of vadastuximab talirine will be reported to the sponsor, regardless of causality. Patients who undergo subsequent allo-SCT within 180 days of the last dose of vadastuximab talirine in the absence of relapse and additional therapy will be followed for SOS/VOD for 100 days post-transplant (Section 7.6.2.4 Adverse Events of Special Interest).

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

Only patients who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study.

Patient medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications.

7.2 Response/Efficacy Assessments

Treatment response will be assessed by pathology review of bone marrow aspirate/biopsy and flow cytometry analysis of the number of blasts in bone marrow at protocol-specified time points (Section 6, Appendix A, Appendix B). Institutional standard frequency is sufficient for response status assessment in long-term follow up.

CBC and differential will also be used to assess the presence of blasts in peripheral blood as well as the extent of hematopoietic recovery of platelets, erythrocytes, and leukocytes, including neutrophils.

Clinical response will be determined at each assessment according to a modification of the response categorization in the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia (Cheson 2003). The category of CR with incomplete platelet recovery (CRp), which has been reported in prior AML trials, will be combined with CRi.

MRD will be assessed at a central laboratory by multiparametric flow cytometry of bone marrow samples obtained as described in Table 4, Table 5, and Table 6 and in the Research Specimen Manual (Walter 2011).

Patients' clinical data must be available for CRF source verification. Copies of bone marrow reports including flow cytometry reports must be made available for review by the sponsor (or its designee), upon request. Bone marrow slides will be made available for central pathology review if requested.

7.3 Pharmacokinetic and ATA Assessments

Blood samples for PK and ATA assessment will be collected at the time points outlined in Table 4, Table 5, and Table 6. Sensitive, qualified assays will be used to measure concentrations of ADC (vadastuximab talirine) and SGD-1882 in plasma and ATA in serum. Remaining PK samples will be archived for possible analysis of vadastuximab talirine - related species. The assays will include enzyme-linked immunosorbent assays (ELISA) and LC-MS/MS assays, as well as other assays if further characterization is required. A qualified electrochemiluminescence assay will be used to assess ATA.

7.4 Biomarker Studies

Sampling timepoints are listed in Table 4, Table 5, and Table 6.

Peripheral blood and bone marrow aspirates will be collected at the time points outlined in Table 4, Table 5, and Table 6. Biomarker assessments may include CD33 expression level and saturation by vadastuximab talirine on CD33+ cells, cytogenetic abnormalities and/or mutation of genes with known prognostic significance for AML, soluble CD33, lymphocyte subset recovery post-transplant, and evaluation of MRD at protocol specified time points.

Table 4: Part A pharmacokinetic, ATA, and biomarker time points for blood

Cycle	Study Day	Time	Window	PK	ATA	sCD33 & Research	CD33 RO & Expression	Lymphocyte Subset Recovery (TBNK)[B]	Research
Pre-allo	Day –28 to –14	Baseline	NA						X
	Day –14	Pre-dose	Within 24 hr prior to vadastuximab talirine dose	X	X	X	X		
		End of IV flush	Within 15 min	X			X		
		2 h	± 15 min	X					
		6 h	± 2 hr	X			X		
	Day –13	24 h	± 4 hr	X					
	Day –11	72 h	± 4 hr	X			X		
	Day –7	168 h	± 24 hr	X		X	X		
	Day –1	312 h	Up to 24 hr pre-transplant	X	X	X			
	Day 30		(±2days)					X	X
	Long-term follow up	Every 3 mos [A]	±2 weeks						

A Every 3 months (±2 weeks) for the first year from transplant; subsequently, every 6 months (±2 weeks) until 3 years post-transplant. No longer required once progression is documented.
B Collected for local laboratory assessment. Window ±3 days.

Table 5: Part A pharmacokinetic and biomarker time points for bone marrow

Cycle	Study Day	Window	Aspirate, MRD	Aspirate, CD33 Expression	Aspirate for Research	Aspirate for PK & sCD33
Pre-allo	Day –28 to –14	Baseline		X	X	X
	Day –1	Up to 24 hr pre-transplant	X			X[C]
	Day 30	(±2days)	X		X	
	Long-term follow up	Every 3 mos[A, B]				

A Every 3 months (±2 weeks) for the first year from transplant; subsequently, every 6 months (±2 weeks) until 3 years post-transplant. No longer required once progression is documented.
B Submit sample for assessment upon disease progression and whenever bone marrow examination is conducted.
C Sample only required for PK

Table 6: Part B pharmacokinetic, ATA, and biomarker time points for blood and bone marrow

Sample Origin				Blood					Bone marrow	
Cycle	Study Day	Time	Window	PK	ATA	sCD33 & Research	CD33 RO & Expression	Lymphocyte Subset Recovery (TBNK)[D]	MRD	Research
NA		Baseline	D –14 to 1						X	X
1	Day 1	Pre-dose	Within 24 hr prior to vadastuximab talirine dose	X	X	X	X	X		
		End of IV flush	Within 15 min	X						
		2 h	±15 min	X						
		6 h	±2 hr	X						
	Day 2	24 h	±4 hr	X						
	Day 4	72 h	±4 hr	X						
2	Day 1	Pre-dose	Within 8 hr prior to vadastuximab talirine dose	X	X	X		X		
		End of IV flush	Within 15 min	X						
3+	Day 1	Pre-dose	±2 weeks						X[B, C]	X[B, C]
			Within 8 hr prior to vadastuximab talirine dose		X[A]	X[A]		X[A]		
		End of IV flush	Within 15 min	X[A]						
EOT			42 to 49 days post-study treatment	X	X	X	X	X	X[C]	X[C]
LTFU		Every 3 months	±2 weeks							

A Day 1 of Cycle 3 and every 2 cycles while on treatment.
B Every 3 months (±2 weeks) for the first 2 years after receiving the first dose of study treatment (Day 1 of Cycle 3 and every other cycle thereafter while on treatment) and then every 6 months (±2 weeks) until 3 years post-transplant. No longer required after disease progression is documented.
C Submit sample for assessment upon disease relapse and whenever a bone marrow examination is conducted.
D Collected for local laboratory assessment. Window ±3 days .

7.4.1 CD33 Expression and Saturation

Total CD33 expression level will be assessed in peripheral blood and bone marrow blasts obtained throughout the study using flow cytometry analysis at a central laboratory, as will detection of free CD33 on the surface of leukemic blasts, (i.e., unoccupied by vadastuximab talirine). Samples will be obtained at the time points specified in Table 4, Table 5, Table 6, and in the Research Specimen Manual. All samples will be assessed at a central laboratory using flow cytometry analysis.

7.4.2 Lymphocyte Subset Recovery

Recovery of T-, B- and NK-cell lymphocyte subsets post-transplant will be monitored in peripheral blood by the local laboratory according to institutional standard.

7.4.3 Cytogenetics and Gene Mutations

Cytogenetic abnormalities and/or mutation of genes with known prognostic significance for AML (e.g., NPM1, FLT3, WT1, and MLL), will be assessed by a local laboratory and correlated with the vadastuximab talirine treatment outcome.

Local laboratory assessment of cytogenetics and gene mutation will be conducted according to the institutional standard. Cytogenetic risk groups will be categorized according to the Medical Research Council classification (Grimwade 1998), and according to European LeukemiaNet (Dohner 2010). Scanned copies or photocopies of all available source documentation for each assessment will be submitted to the sponsor. Any additional mutational data obtained beyond those required for risk categorization will be included in this report.

7.5 Biospecimen Repository

For patients who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Seattle Genetics and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of ADC sensitivity and resistance mechanisms, and to identify biomarkers of ADCs. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed following study completion.

7.6 Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of adverse events (AEs) including serious adverse events (SAEs), recording of concomitant medication and measurements of protocol-specified physical examination findings and laboratory tests.

Safety will be monitored over the course of the study by an SMC as described in Section 3.1.

7.6.1 GVHD Assessments

For patients in Part A, GVHD assessment will be performed at Day 30, 3, 6, and 12 months post-transplant, and every 6 months thereafter (see Section 6.1 and Appendix A).

For patients in Part B, a history and physical exam to assess GVHD will be performed at baseline prior to the start of treatment with vadastuximab talirine, and on Day 1 of every cycle (see Section 6.2 and Appendix B).

GVHD evaluation and grading will be performed according to the GVHD Target Organ Staging (Harris 2016); refer to Appendix F.

7.6.2 Adverse Events

7.6.2.1 Definitions

Adverse Event

According to the International Conference on Harmonization (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events and Pre-existing Conditions CRF:

- From the time of informed consent prior to the first dose of vadastuximab talirine [Part A: D −14 and Part B: D1], only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing at time of first study drug dose [Part A: D −14 and Part B: D1] should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from the first dose of vadastuximab talirine [Part A: D −14 and Part B: D1] (during and postdose) through the end of the safety reporting period (see Section 7.6.2.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical

condition rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	Resulted in a persistent or significant incapacity or substantial disruption of the patient's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

Adverse Event Severity

AE severity should be graded using the NCI CTCAE, version 4.03. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for Serious Adverse Events).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (vadastuximab talirine, fludarabine, melphalan, tacrolimus, or methotrexate) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) • an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

7.6.2.2 Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during patient questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events and Pre-existing Conditions CRF:

- Description including onset and resolution dates
- Whether it met serious criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For infusion-related reactions, do not use the NCI CTCAE terms of 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or hypersensitivity reaction.' Instead, record each sign or symptom as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and an SAE form.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.

- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of the Underlying Cancer

Do not use the term 'disease progression' alone when reporting AEs, including SAEs, because it is too nonspecific. Symptoms of disease progression that meet the criteria for an SAE must be reported. When possible, report the specific disease (clinical) manifestation of the progression (e.g., 'malignant pleural effusion', 'spinal bone metastases', 'lymphadenopathy', 'brain metastases'). Otherwise, it is acceptable to report the specific disease (e.g., non-Hodgkin lymphoma) as an SAE.

Pregnancy

Notification to Drug Safety: Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 6 months after the last dose of study drug(s) including any pregnancies that occur in the partner of a male study patient. Only report pregnancies that occur in a male patient's partner if the estimated date of conception is after the male patient's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 48 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of data on the CRF: All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s) will also be recorded on the Adverse Events and Pre-Existing Conditions CRF.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.6.2.1) should be reported as SAEs.

7.6.2.3 Reporting Periods for Adverse Events and Serious Adverse Events

Part A: The safety reporting period for all AEs and SAEs is from study Day –14 (predose) through Day 30 or the EOT visit after the last study treatment, whichever is later; although, all study protocol-related AEs are to be collected from the time of informed consent. SAEs and events of special interest that occur from Day 31 to Day 100, regardless of relation to study drug, should be reported to the sponsor immediately. Events of special interest are those that meet the following criteria:

- Any pulmonary event not related to infection with interstitial changes requiring mechanical ventilation
- Any renal event requiring dialysis, nephrostomy or surgical procedure
- Severe hepatic dysfunction (including SOS/VOD and hepatic acute Graft vs Host Disease); see Section 7.6.2.4

- Sudden cardiac death, fatal myocardial infarction, heart failure unresponsive to medical management
- Sepsis and septic shock

Events of special interest considered by the investigator to be study drug related will be expedited. All SAEs that occur after the safety reporting period and are considered related to study treatment in the opinion of the investigator should also be reported to the sponsor.

Deaths occurring up to Day 100 post-transplant, regardless of causality or relation to study drug, should be reported to the sponsor immediately.

Part B: The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through the EOT visit or Day 42 after the last study treatment, whichever is later; although, all study protocol-related AEs are to be collected from the time of informed consent. All SAEs occurring after the safety reporting period that are considered study treatment related in the opinion of the investigator should be reported to the sponsor. Events of special interest (as listed above) occurring after the safety reporting period up to Day 100 post-transplant, regardless of relation, should be reported to the sponsor immediately. Deaths occurring up to Day 100 post-transplant, regardless of causality or relation to study drug, should be reported to the sponsor immediately.

Part A and Part B: SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, the patient dies or withdraws consent, or study closure. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

7.6.2.4 Adverse Events of Special Interest

Hepatobiliary serious adverse events, including cases of SOS/VOD, are considered adverse events of special interest, regardless of causality. Investigators must complete a detailed "Liver Disease Adverse Event Information Form" for all of these events. All reported adverse events of special interest will be subject to expedited reporting. Additionally, they should be reported to the sponsor if they occur as part of long term follow-up regardless of causality. Events of SOS/VOD that occur within 180 days of the last dose of vadastuximab talirine will be reported. For patients who undergo subsequent allogeneic stem cell transplant in the absence of relapse and additional therapy, patients will be followed for SOS/VOD for 100 days post-transplant.

7.6.2.5 Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE, investigators are to report the event to the sponsor, regardless of the relationship of the event to the study treatment regimen.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Patient number
- Date of event onset
- Description of the event
- Study treatment, if known

The completed SAE form and SAE Fax Cover Sheet are to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email address or fax number specified on the SAE report form).

Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.

7.6.2.6 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section 7.6.2.4).

The sponsor will report all SAEs to regulatory authorities as required per local regulatory reporting requirements. In the United States, endpoints that assess disease-related mortality or major morbidity as well other SAEs that are not study endpoints, but are known consequences of the underlying disease or condition that are anticipated to occur in the study population should not be reported to the Food and Drug Administration (FDA) as individual IND safety reports per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's final guidance Safety Reporting Requirements for INDs and BA/BE Studies (December 2012).

In this study, SAEs of leukemic relapse do not require individual IND safety reports. Events of febrile neutropenia are anticipated in this population and individual IND safety reports will not be submitted to the FDA.

These anticipated SAEs will be reviewed periodically by the Seattle Genetics Drug Safety Department. If, upon review, these SAEs are occurring at a higher rate than that which would be expected for the study population, then IND safety reports for the SAE will be submitted to the FDA.

7.6.3 Clinical Laboratory Tests

Samples will be drawn for both central and local labs. Local laboratory testing will include institutional standard tests for evaluating safety and making clinical decisions, and will not necessarily include all of the analytes required in the central evaluation. The following laboratory assessments will be performed by the central lab to evaluate safety at scheduled timepoints (see Appendix A and Appendix B) during the course of the study:

- The chemistry panel is to include the following tests: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, calcium, creatinine, chloride, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, uric acid, lipase, and amylase.

- The CBC with differential is to include the following tests: white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, blasts, hemoglobin, and hematocrit.

The following laboratory assessment(s) will be performed by local laboratories at scheduled timepoints (see Appendix A and Appendix B) during the course of the study:

- A serum or urine β-hCG pregnancy test for females of childbearing potential
- Urinalysis with reflexive microscopy – samples will be tested for creatinine. These laboratory results will be used to calculate a urine protein:creatine (UPC) ratio.
- T-, B- and NK-cell lymphocyte subsets

7.6.4 Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. For adult patients only, measurements of height obtained within the prior 12 months may be utilized.

7.7 Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

The Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia (Cheson 2003) will be used to categorize any antitumor activity observed. These criteria are considered standard in oncological practice, and the intervals of evaluation in this protocol are appropriate for disease management. The one-year survival rate will also be used to categorize the safety and antitumor activity observed. This is a standard measurement post allogeneic transplant for patients with AML.

ATA is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to vadastuximab talirine. Pharmacokinetic assessments for drug activity are also common in clinical studies.

Exploratory biomarker measurements in peripheral blood samples to enable correlation with pharmacokinetic assessments are common in clinical studies. Assessments conducted on bone marrow aspirates are also common in clinical studies of AML. The majority of bone marrow biomarker samples are to be collected at times when bone marrow examination is already indicated for disease assessment.

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of patients at the site, Seattle Genetics or its designated

clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current Investigator's Brochure/package insert
- Recording and reporting AE and SAE
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval process
- Informed consent process
- GCP guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing and record keeping
- Patient coding and randomization (if applicable)
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Seattle Genetics representative will review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study patients, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by Seattle Genetics or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2 Data Management Procedures

Seattle Genetics will provide CRF Completion Guidelines for electronic CRF (eCRF) data entry. Study-specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3 Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect patient confidentiality are to be employed during monitoring. The CRFs and related source documents will be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information contained in the CRFs, such as disease assessments, AEs, and concomitant medications, is complete and correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities.

8.4 Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness by the designated monitor(s) during monitoring visits to the study centers. Any discrepancies will be resolved with the investigator or designees as appropriate.

8.5 Quality Assurance Procedures

The Research and Development Quality group or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Research and Development Quality group of Seattle Genetics as part of the written record.

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

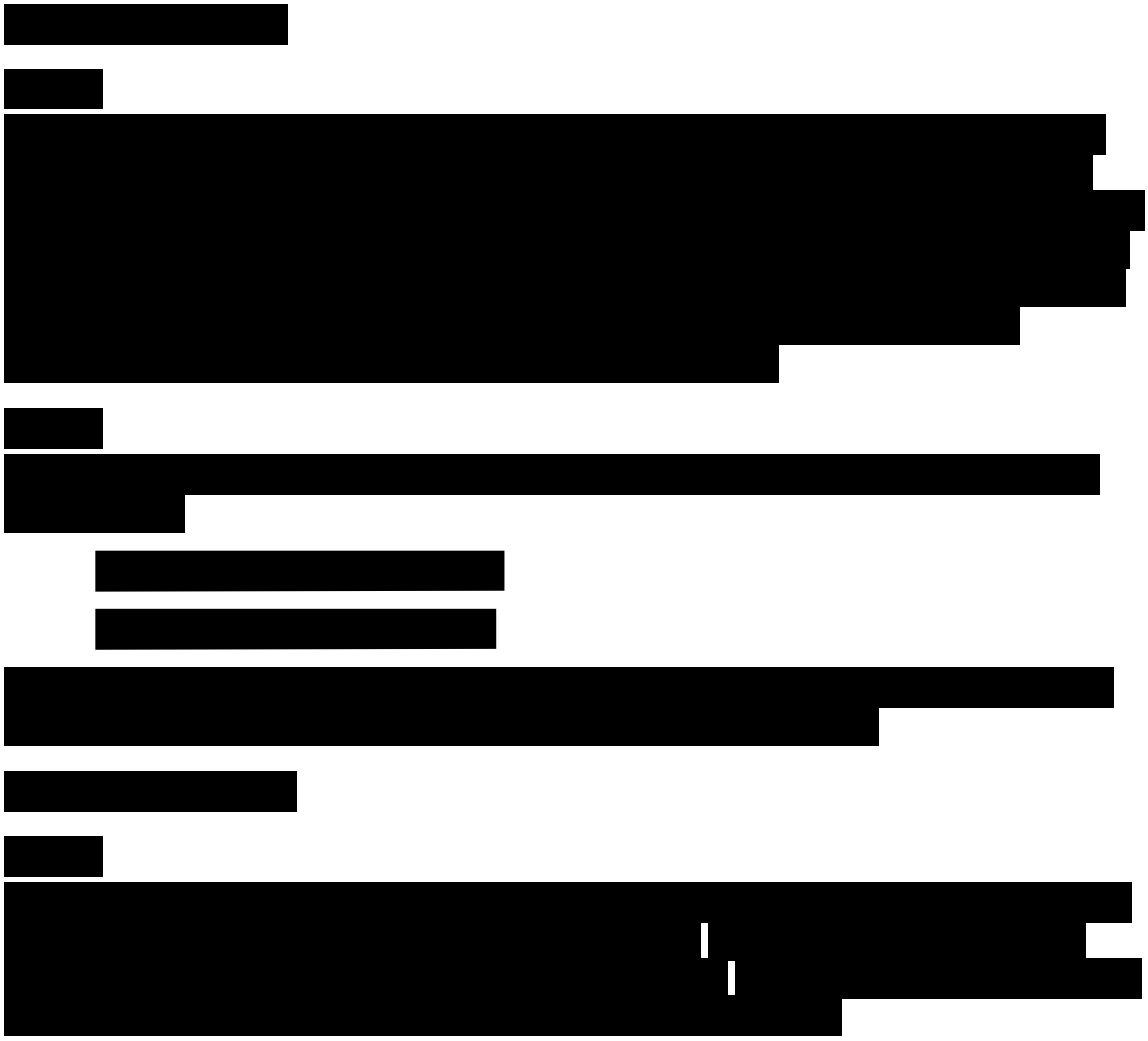
Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2 Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and institution in which the study will be conducted, or for the period specified by Seattle Genetics, whichever is longer. The investigator must contact Seattle Genetics prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee (such as another investigator or IRB/IEC). Notice of such transfer will be provided in writing to Seattle Genetics, Inc.

9 DATA ANALYSIS METHODS

9.1 Determination of Sample Size



[redacted]

9.2 Study Endpoint Definitions

Study endpoints are presented in Section 2.4. The endpoints that need to be defined are presented in this section.

9.2.1 Overall Survival (OS) and One-year Survival Rate

OS is defined as the time from the day of alloSCT to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive. Patients lacking data beyond the day of first dose will have their survival time censored at 1 day.

One-year survival rate will be estimated by Kaplan-Meier method.

9.2.2 Minimal Residual Disease (MRD) Negativity Rate

The MRD negativity rate is defined as the proportion of patients with MRD negativity.

9.2.3 Best Response

The best response is defined as the best disease response determined by the investigator during the study.

9.2.4 Duration of Response

Duration of response is defined as the time from the start of the first documented CR/CRi to the first documentation of relapse or death due to any cause, whichever comes first. Duration of response will be censored on the date of the last disease assessment documenting absence of progressive disease (PD) for patients who have not progressed and are still on study at the time of analysis, who have received antitumor treatment other than the study treatment, or have been removed from study prior to documentation of PD. Duration of response will only be calculated for the patients achieving CR/CRi.

9.2.5 Event-free Survival (EFS)

Event-free survival is defined as the time from the day of alloSCT to the first documentation of treatment failure (defined below). Censoring for EFS is the same as that for duration of response.

Part A

Treatment failure is defined as failure to achieve CR/CRi by Day 30, relapse from CR/CRi, or death, due to any cause, whichever comes first.

Part B

Treatment failure is defined as relapse of AML or death due to any cause, whichever comes first.

9.3 Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (e.g., adding baseline assessments to define a subgroup). The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.3.1 General Considerations

Part A and Part B will be summarized separately.

9.3.1.1 Randomization and Blinding

This is an open-label, non-randomized study. Blinding is not applicable.

9.3.1.2 Adjustments for Covariates

Adjustments for covariates are not planned for this phase 1/2 study.

9.3.1.3 Handling of Dropouts and Missing Data

In general, missing data will not be imputed. Patients with missing values of a variable other than the time-to-event endpoints (OS, duration of response, and EFS) will be excluded from the analysis of that endpoint. Censoring rules will be applied to the estimation of the distribution of the time-to-event endpoints, details will be provided in the SAP.

9.3.1.4 Multicenter Studies

Due to the expected small number of patients in each site, adjustments for sites are not planned. Descriptive summary of selected variables or endpoints by site may be provided.

9.3.1.5 Multiple Comparisons and Multiplicity

No adjustments for multiple comparisons are planned.

9.3.1.6 Data Transformations and Derivations

Time variables based on two dates, (e.g., Start Date and End Date), will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section.

Baseline values used in all statistical analyses will be the most recent measurement prior to the first dose of vadastuximab talirine.

For Part A, Day 0 is defined as the date of the alloSCT. For Part B, Day 1 is defined as the first dose of vadastuximab talirine.

9.3.1.7 Analysis Sets

All Treated Patients Set

The all treated patients analysis set includes all patients who receive any positive amount of vadastuximab talirine.

DLT-Evaluable Set

The DLT-evaluable analysis set includes all treated patients who received vadastuximab talirine and either experienced a DLT or were followed for the full DLT evaluation period.

9.3.1.8 Examination of Subgroups

All analyses will be presented by dose level and study part.

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

9.3.1.9 Timing of Analyses

Each part of the study will be conducted separately. For phase 1 portion of the study, data will be evaluated for dose-escalation for each dose cohort. Formal interim analysis of the phase 2 data is not planned. The final analysis of the study will be conducted after all patients have been followed for 5 years after the last patient is enrolled, or until study closure, whichever occurs first.

In addition, interim data from the study may be presented at scientific meetings such as the American Society of Hematology (ASH) or the American Society of Clinical Oncology (ASCO).

9.3.2 Patient Disposition

An accounting of study patients by disposition will be tabulated and the number of patients in each analysis set will be summarized. Patients who discontinue study treatment and patients who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

9.3.3 Patient Characteristics

Demographics and other baseline characteristics will be summarized. Details will be provided in the SAP.

9.3.4 Treatment Compliance

The dose administered at each cycle will be assessed and dose intensity will be summarized. Details will be provided in the SAP.

9.3.5 Efficacy Analyses

Efficacy analyses will be performed by cohort and study part using the all treated patients set.

The one-year survival rate and its 95% confidence interval will be estimated by Kaplan-Meier method. OS, duration of response and EFS will be analyzed using Kaplan-Meier method. Median time will be calculated, where possible, with 95% confidence intervals.

The best response rate and the MRD negativity rate will be provided with their 95% confidence intervals.

Detailed methodology will be provided in the SAP.

9.3.6 Pharmacokinetic and ATA Analyses

The PK of vadastuximab talirine ADC and SGD-1882 (if measurable) will be evaluated by noncompartmental analysis. The following PK parameters will be evaluated, as appropriate:

- Area under the curve (AUC)
- Concentration at the end of infusion (C_{eoi}) or maximum observed concentration
- (C_{max})
- Trough concentration (C_{trough})
- Terminal or apparent terminal half-life ($t_{1/2}$)
- Systemic clearance and volume of distribution at steady state

The incidence of ATA will be summarized by descriptive statistics.

9.3.7 Biomarker Analyses

Biomarker assessments and relationship to clinical and biological variables will be summarized using descriptive statistics. The relationship of vadastuximab talirine PK and relevant biomarkers, safety, or efficacy may be explored. The relationship of exploratory endpoints to clinical activity may be explored. These analyses, if conducted, will be descriptive.

9.3.8 Other Analyses

Not applicable.

9.3.9 Safety Analyses

9.3.9.1 Extent of Exposure

Duration of treatment, number of cycles (for Part B only), total dose and dose intensity will be summarized by dose cohort and study part. Dose modifications will also be summarized. Details will be provided in the SAP.

9.3.9.2 Adverse Events

Adverse events will be defined as treatment emergent if they are newly occurring or worsen following study treatment. The incidence of all AEs, treatment-emergent AEs, and treatment-related AEs will be tabulated. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be listed and summarized by study part, dose cohort, MedDRA preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in one patient, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term and treatment group. AEs leading to premature discontinuation of study drug will be summarized and listed in the same manner.

In addition, AEs will be summarized by the Bearman Toxicity Criteria (Bearman 1988).

9.3.9.3 Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.9.4 Clinical Laboratory Results

Laboratory values (e.g., chemistry, hematology, urinalysis, and pulmonary function tests) may be presented graphically for each lab test by scheduled visit. Summary statistics may be tabulated where appropriate. Laboratory values will be listed with NCI CTCAE v4.03 grades and out-of-normal range flags.

9.3.9.5 Other Safety Analyses

ECOG Status

ECOG status will be summarized by visit.

9.3.10 Interim Analyses

No interim analyses are planned. See Section 9.3.1.9 for the timing of the analyses.

10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

10.1 Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the IRB/IEC approved informed consent document and for ensuring patients are re-consented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each patient, or legally authorized representative, if applicable to this study, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

If informed consent is obtained from a legally authorized representative for a patient who is unable to provide informed consent at study entry (if applicable), but the patient is later able to provide informed consent, the investigator must obtain written informed consent from the patient.

10.2 Ethical Review

The investigator will provide the sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical Investigator's Brochure and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The investigator must provide the following documentation to the sponsor or its designee:

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3 Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on GCP, and all applicable local and/or regional laws, rules, and regulations.

10.3.1 Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators and name and address of the research facilities are included in the investigator file.

10.3.2 Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study patient) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling patients who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.4 Study Documentation, Privacy and Records Retention

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested,

the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing patient medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the patient authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of patient identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

10.5 Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

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APPENDIX A: SCHEDULE OF EVENTS PART A: PRE-ALLO SCT

		Screening/ Baseline			Enrollment										EOT[A]	Long-term F/U[M]
	Day	–44 to –14	–28 to –14	–21 to –14	**Within 7 days of first dose**	**D –14**	**D –13**	**D –11**	**D –7**	**D –5 to –2**	**D –1**	**D 0**	**D 7, D 14, D 21**	**D 30**	**30–37 days post-transplant**	
	Visit Window													±2 days		±2 wks
Screening and Safety Assessments	Inclusion/Exclusion, patient history	X			Submit confirmation prior to treatment											
	Informed consent	X														
	Medical History	X														
	Physical exam with weight			X		X[C]									X	
	CMV antibody test	X[E]														
	HCT-specific comorbidity index	X[E]														
	HIV and HTLV1 I/II antibody test	X[E]														
	Serum chemistry panel			X		X[C]			X			X	X	X	X[K]	
	CBC with differential			X		X[C]			X			X	X	X	X[K]	
	Urine creatinine clearance	X[E]														
	Spot urine for protein and creatinine	X[E]							X					X		
	Pregnancy test			X[L]											X[L]	
	ECHO/MUGA	X[E]														
	DLCO and FEV1	X[E]														
	Herpes simplex	X[E]														
	Varicella zoster virus	X[E]														
	Hepatitis panel	X[E]														
	ECOG performance status			X		X									X	
	GVHD assessments													X		X[F]
	Concomitant medications	Related to study procedures				Collect from predose D –14 to D 30 post-transplant or EOT whichever is later										
	Adverse event collection[G]															
Treatment	Vadastuximab talirine administration					X										
	RIC treatment[H]									X[D]						
	Allogeneic SCT											X				
	Tacrolimus[H]										Start D-1[H]					
	Methotrexate[H]												Start D1[H]			
Samples	Samples for PK, ATA, and biomarker testing[I,J]		X			X	X	X	X		X			X		
	Chimerism assay per institutional guidelines.													X		
Response Assessment	BM Aspirate for MRD Assessment[J]										X			X		
	BM examination		X											X		
	Contact for survival status and subsequent therapies															X[B]

A EOT eval. obtained before initiation of nonprotocol therapy. If EOT eval is completed before 30 days after transplant, the site will conduct a phone screen 30 –37 days after transplant to ensure no changes in AE profile.

B LTFU (consisting of a phone call for survival and collection of subsequent therapy information when a clinic visit is not required) will occur every month (±1 wk) from transplant for the first 2 years, and then every 3 months (±2 wks) until death or study closure. See Section 6.1.15.

C May be obtained within 24 hrs prior to dose; does not need to be repeated if done within 24 hrs prior.

D Fludarabine 30 mg/m^2/day on Day –5 to Day –2 (total dose of 120 mg/m^2). Melphalan 140 mg/m^2 on Day –2

E Does not need to be repeated if performed within 42 days of enrollment.

F Every 3 mos (±2 wks) from transplant for the 1st yr and then every 6 mos (±2wks) until 3 yrs post-transplant. No longer required once progression is documented.

G See Section 7.6.2 for additional information on AE and SAE reporting

H See Section 5.1 for details

I Please see Table 4, Section 7.4

J Please see Table 5, Section 7.4

K Does not need to be repeated if done within 7 days prior.

L Females of childbearing potential only.

M See Section 6.1.15 and 7.6.2.4

APPENDIX B: SCHEDULE OF EVENTS PART B: POST-ALLO SCT

		Baseline/ Screening			Enrollment	Cycle 1								Cycle 2	Cycle 3+	EOT (42 to 49 days post-study treatment)	Long-term F/U[K]
						D1	D2	D4	D8	D15	D22	D28	D42	D1	D1		
	Visit Window	D –28 to 1	D –14 to 1	D –7 to 1	D –7 to 1				±1D	±1D	±1D	±1D	±1D				±2 wks
Baseline and Safety Assessments	Inclusion/exclusion	X			Eligibility documentation submitted to sponsor prior to study start												
	Informed consent	X															
	Medical history and transplant details	X															
	Physical exam with weight			X		X[C]								X[C]	X[C]		
	Pregnancy test[J]			X												X	
	ECOG performance status			X												X	
	Serum chemistry panel			X		X[C]			X	X	X	X	X[E]	X	X	X	
	CBC with differential			X		X[C]			X	X	X	X	X[E]	X	X	X	
	Spot urine for protein and creatinine			X												X	
	GVHD assessment	X				X[A]								X[A]	X[A]	X	X[A]
	Con meds & AEs[H]	Collect any related to study protocol procedures					Collect from pre-dose D1 to 42 days after study treatment or EOT, whichever is later										
Treatment	Vadastuximab talirine administration					X								X	X		
Samples	Samples for PK, ATA, and biomarkers[F]		X			X	X	X						X	X	X	
Response Assessments	BM examination		X												X[G]	X[D]	
	BM aspirate for MRD		X												X[G]	X[D]	
	Contact for survival status and subsequent therapies																X[B]

A Day 1 of all cycles and in the absence of disease progression, continue to assess on the same schedule as BM examinations in follow-up.

B LTFU (consisting of a phone call for survival and collection of subsequent therapy information when a clinic visit is not required) will occur every 1 month (±1 wk) for the first 2 years after receiving the first dose of study treatment, and then every 3 months (±2 wks) until death or study closure. See Section 6.2.10.

C May be obtained within 24 hours prior to dose; does not need to be repeated if done within 24 hours prior.

D If not done within 42 days prior to EOT assessment.

E Not required if ANC recovers ≥1000 and platelets recover to ≥50,000.

F See Table 6

G Every 3 mos (±2 wks) for the first 2 years year after dosing (approximately every 2 cycles while on treatment) and then every 6 mos (±2 wks) until 3 years post-transplant.

H See Section 7.6.2 for additional information on AE and SAE reporting

I Continue to be obtained on the schedule described in Footnote G. No longer required after disease progression is documented.

J Females of childbearing potential only.

K See Section 6.2.10 and 7.6.2.4

APPENDIX C: PERFORMANCE STATUS SCALES CONVERSION

Karnofsky		Lansky		ECOG	
Percent	Description	Percent	Description	Score	Description
100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.		
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.	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).
70	Cares for self, unable to carry on normal activity or to do active work.	70	Both greater restriction of, and less time spent in, play activity.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.	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.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet active play and activities.		
40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.		
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.		
0	Dead.	0	Dead.	5	Dead.

APPENDIX D: NEW YORK HEART ASSOCIATION CLASSIFICATION

A Functional and Therapeutic Classification for Prescription of Physical Activity for Cardiac Patients

Class I: Patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II: Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III: Patients with marked limitation of activity; they are comfortable only at rest.

Class IV: Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Online source:

Classes of Heart Failure, http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp. Accessed August 25, 2015.

APPENDIX E: BEARMAN REGIMEN-RELATED TOXICITY ACCORDING TO ORGAN SYSTEM

	Grade I	Grade II	Grade III
Cardiac toxicity	Mild EKG abnormality, not requiring medical intervention; or noted heart enlargement on CXR with no clinical symptoms	Moderate EKG abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestive heart failure responsive to digitalis or diuretics	Severe EKG abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention; or decrease in voltage by more than 50%
Bladder toxicity	Macroscopic hematuria after 2 d from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 d from last chemotherapy dose not caused by infection; or hematuria after 2 d with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedure
Renal toxicity	Increase in creatinine up to twice the baseline value (usually the last recorded before start of conditioning)	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
Pulmonary toxicity	Dyspnea without CXR changes not caused by infection or congestive heart failure; or CXR showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	CXR with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by Infection or CHF; or decrease of P02 (> 10% from baseline) but not requiring mechanical ventilation or >50% 0_2 on mask and not caused by infection or CHF	Interstitial changes requiring mechanical ventilatory support or >50% oxygen on mask and not caused by infection or CHF
Hepatic toxicity	Mild hepatic dysfunction with 2.0 mg% s bilirubin s 6.0mg%; or weight gain >2.5% and <5% from baseline, of noncardiac origin; at SGOT increase more than 2-fold but less than 5-fold from lowest preconditioning	Moderate hepatic dysfunction with bilirubin >6 mg% <20 mg%; or SGOT increase >5-fold from preconditioning; or clinical ascites or image documented ascites >100 mL; or weight gain >5% from baseline of noncardiac origin	Severe hepatic dysfunction with bilirubin >20 mg%; or hepatic encephalopathy; or ascites compromising respiratory function

	Grade I	Grade II	Grade III
CNS toxicity	Somnolence but the patient is easily arousable and oriented after arousal	Somnolence with confusion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding, or CNS infection	Seizures or coma not explained (documented) by other medication, CNS infection, or bleeding
Stomatitis	Pain and/or ulceration not requiring a continuous IV narcotic drug	Pain and/or ulceration requiring a continuous IV narcotic drug (morphine drip)	Severe ulceration and/or mucositis requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation
Gl toxicity	Watery stools >500 mL but <2,000 mL every d not related to infection	Watery stools >2,000 mL every d not related to infection; or macroscopic. hemorrhagic stools with no effect on cardiovascular status not caused by infection; or subileus not related to infection	Ileus requiring nasogastric suction and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion

(Bearman 1988)
NOTE. Grade IV regimen-related toxicity is defined as fatal toxicity.
Abbreviations: CXR, chest x-ray; IV, intravenous

APPENDIX F: GVHD TARGET ORGAN STAGING

Stage	Skin (Active Erythema Only)	Liver (bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	< 2 mg/dl	No intermittent nausea, vomiting, or anorexia	<500 mL/day or <3 episodes/day
1	Maculopapular rash< 25% BSA	2–3 mg/dl	Persistent nausea, vomiting or anorexia	500–999 mL/day or 3-4 episodes/day
2	Maculopapular rash 25–50% BSA	3.1–6 mg/dl		1000–1500 mL/day or 5-7 episodes/day
3	Maculopapular rash >50% BSA	6.1–15 mg/dl		>1500 mL/day or >7 episodes/day
4	Generalized erythroderma (>50% BSA) *plus* bullous formation and desquamation >5% BSA	>15 mg/dl		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based on most severe target organ involvement):

Grade 0:	No Stage 1-4 of any organ.
Grade 1:	Stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade 2:	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
Grade 3:	Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI
Grade 4:	Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.

(Harris 2016)

APPENDIX G: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled A phase 1/2 study of vadastuximab talirine administered in sequence with allogeneic hematopoietic stem cell transplant in patients with relapsed or refractory acute myeloid leukemia (AML)

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature	Date

Investigator Name, Printed

APPENDIX H: DOCUMENT HISTORY

Version	Date
Original	25-Aug-2015
Amendment 1	16-Feb-2016
Amendment 2	12-Oct-2016
Amendment 3	15-Mar-2017

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
Title page	Medical monitor and contact info has been updated from [redacted]	[redacted] update medical staff info.
2.1, 2.2 2.4.2, Synopsis	Clarified that objectives and endpoints for rate of MRD negativity, best response on treatment, and duration of response are applicable to Part A only.	Clarification.
3.1.1, 6.1.15, Appendix A, Synopsis	Clarified the response assessment schedule for Part A: Patients will be evaluated for response at Day 30 and every 3 months from transplant for 1 year and then every 6 months until 3 years post-transplant (no longer required once disease progression is documented).	Clarification.
3.1.1	Added a possible Dose Level -1 to Part A (30 mcg/kg), to be studied only upon SMC recommendation.	Additional dose level to allow possible dose exploration at lower vadastuximab talirine doses.
3.1.2, 6.2.10, Appendix B, Synopsis	Clarified the response assessment schedule for Part B: Response assessments will be every 3 months after the first dose of study drug for 2 years (every other cycle during treatment), and then every 6 months until 3 years post-transplant.	Clarification.
4.1, Criterion 1, Synopsis	Added/clarified requirements for confirmation of patient eligibility: • Relapsed/refractory AML • Part A: ◦ Clarified number of previous induction regimens required ◦ Specified the risk factors that would cause a patient to be eligible after only 1 induction regimen • Part B: ◦ Clarified conditioning regimen permitted ◦ Specified that CR/CRi must be documented within 14 days of first dose of study treatment	To ensure patient eligibility for the study.
4.1, Criterion 4	Specified total bilirubin measurement required at baseline.	Clarification of criterion.
4.1, Criterion 8 and 9, Synopsis	Added criteria for baseline left ventricular ejection fraction, DLCO, FEV1, and FVC.	To ensure patient safety.

Section(s)	Change	Rationale
4.2, Criterion 6	The following changes: • Current therapy is defined as within 14 days prior to first dose of vadastuximab talirine • For Part B, immunosuppressive agents are allowed for prophylaxis against and treatment of GVHD. • Moved following text from Exclusion #2: For Part A, hydroxyurea or 6-mercaptopurine used for cytoreduction may be given up to 1 day prior to treatment	Clarification.
4.2, Criterion 9	Updated to exclude patients with a history of primary invasive malignancy that has not been in remission for 3 years (previously was 1 year), and to exclude patients with any history of metastatic malignancy.	To ensure patient eligibility for treatment with vadastuximab talirine.
4.2, Criterion 10	Clarified that patients with partially matched donors or cord blood cell sources are not eligible in Part A.	Clarification.
4.2, Criterion 11, Synopsis	Patients with a history of VOD requiring defibrotide are not permitted in Part B.	To ensure patient safety.
5.10.2	Specified permitted concomitant therapy: DLI or stem cell boost to treat decreasing engraftment, defibrotide for VOD (Part A), and immunosuppressive agents for GVHD treatment and prophylaxis (Part B).	To permit required concomitant therapy during the study treatment period.
5.10.3	Specified prohibited concomitant therapy: DLI to treat loss of response and sirolimus (Part A). Added exception to treatment with investigational drugs for defibrotide to treat VOD.	Added prohibited concomitant therapies to improve patient safety.
6.1.4, 6.1.9, 6.1.11, 6.1.13, 6.1.14, 6.1.15, 6.2.4, 6.2.9, 6.2.10, 7.4, Appendix A, Appendix B	Clarified assessments and visit schedule (including windows) for each study day, including specifying the start dates for tacrolimus and methotrexate in Part B.	Clarification.
7.4.2, 7.6.3	Specified that lymphocyte subset recovery will be monitored by a local laboratory. Added clarifications regarding central and local laboratory assessments.	Clarification.
7.6.1, Appendix F	GVHD assessment clarifications were added, and a reference to the Modified Keystone Criteria for GVHD grading was provided.	To aid in the grading and assessment of GVHD.
7.6.2, 9.3.9.5	Vital signs sections have been deleted.	Correction.
References	Updated reference for AML standard of care.	Clarification.
Throughout document	Administrative changes and corrections	For clarity.

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
3.1.2,4.1, Synopsis	Patients enrolled to Part B may be dosed between Day 42 and Day 100.	To test the safety of earlier administration of the study drug post-transplantation
3.1.3, 3.1.3.1	Stopping rules added to the trial	To ensure patient safety
4.2	History of locally treated, localized cervical cancer was added to the exempt list of Exclusion criterion #9	To correct an omission from previous version
5.1	Dosing day guidance added for Tacrolimus	Clarification
5.2.3	Redundant language was removed	Guidance already specified in Section 5.1
5.10.2, 5.10.3	Defibrotide allowed for patients in Parts A and B	Approved to treat VOD after previous version
7.4, Table 4, Table 6	Window ±3 days added to TBNK	Clarification
7.6.1, Appendix F	GVHD Target Organ Staging replaced the Modified Keystone Criteria for GVHD grading	Most current grading evaluation is implemented
7.6.2.3	Clarification for AE and SAE reporting periods	To provide clarification and guidance with updated dosing plan and stopping rules
8.5	Updated department name to Research and Development Quality	Administrative change
Appendix A	Footnote "L" was relocated to the correct area on the schedule	To correct an error from previous version.

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
[redacted]	[redacted]	[redacted]
6.1.15, 6.2.10, Appendix A, Appendix B	Long term follow-up amended to decrease the required assessments; clarification added to detail adverse events of special interest	To decrease the burden on patients and follow patients who have received vadastuximab talirine for safety
6.2.9	End of Treatment amended to decrease required assessments	To decrease the burden on patients
7.2	Clarification that institutional standard frequency is sufficient for response status assessment in long-term follow-up.	To decrease the burden on patients and sites
Table 4, Table 5, and Table 6	Sample timepoints removed in long-term follow-up	To decrease the burden on patients since additional sampling is no longer needed
7.6.2.4	Section added: Adverse Events of Special Interest	To ensure the safety of this patient population