A PHASE 1/2 STUDY OF VADASTUXIMAB TALIRINE (SGN-CD33A) IN COMBINATION WITH AZACITIDINE IN PATIENTS WITH PREVIOUSLY UNTREATED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS) INTERMEDIATE-2 OR HIGH RISK MYELODYSPLASTIC SYNDROME (MDS)

Protocol Number: SGN33A-004
Study Phase: 1/2
IND Number: 116300
EudraCT Number: Not applicable

Date and Version: **13 April 2017, Version 03**

Sponsor:
Seattle Genetics, Inc.
Bothell, WA 98021 USA
1-855-473-2436

Clinical Research Organization (CRO):
PRA Health Sciences
4130 ParkLake Avenue, Suite 400
Raleigh, NC 27612 USA

Safety Fax (SAE reporting):
1-425 527-4308
drug.safety@seagen.com

Medical Monitor/ Medical Expert:

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Council for Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

CONFIDENTIAL

1. SIGNATURES

Representatives of Sponsor

I have read and agree to the protocol, SGN33A-004, titled 'A phase 1/2 study of vadastuximab talirine (SGN-CD33A) in combination with azacitidine in patients with previously untreated International Prognostic Scoring System (IPSS) Intermediate-2 or High risk myelodysplastic syndrome (MDS)'. I am aware of my responsibilities under the guidelines of GCP, local regulations (as applicable), and the study protocol. I agree to conduct the study according to these responsibilities.

Investigator

I have read and agree to the protocol, SGN33A-004, titled 'A phase 1/2 study of vadastuximab talirine (SGN-CD33A) in combination with azacitidine in patients with previously untreated International Prognostic Scoring System (IPSS) Intermediate-2 or High risk myelodysplastic syndrome (MDS)'. I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable), and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Clinical Site: _____

Site Number: _____

Site Principal Investigator:

_____ _____

Print Name Title

_____ _____

Signature Date

2. SYNOPSIS

NAME OF SPONSOR: Seattle Genetics, Inc.	**PROTOCOL No.:** SGN33A-004
NAME OF STUDY TREATMENT: Azacitidine with or without Vadastuximab Talirine	
TITLE OF STUDY: A phase 1/2 study of vadastuximab talirine (SGN-CD33A) in combination with azacitidine in patients with previously untreated International Prognostic Scoring System (IPSS) Intermediate-2 or High risk myelodysplastic syndrome (MDS)	
STUDY CENTERS: Subjects will be enrolled at approximately 35 sites in North America.	
STUDY PERIOD: First subject enrolled: May 2016 All subjects completed treatment: May 2019	**PHASE OF DEVELOPMENT:** Phase 1/2

OBJECTIVES:

Primary Objective:

- To determine the recommended vadastuximab talirine (SGN-CD33A) dose in combination with azacitidine in the open-label Phase 1 Portion of study
- To compare the overall response rate (ORR = complete response + partial response [Complete response (CR)+PR]) between treatment arms in the randomized, double-blind, placebo-controlled Phase 2 Portion of study

Secondary Objectives:

- To evaluate the safety of the combination of vadastuximab talirine and azacitidine (Phase 1 and Phase 2 Portions)
- To compare the CR rate between treatment arms (Phase 2 Portion)
- To compare the hematologic improvement (HI) rate between treatment arms (Phase 2 Portion)
- To compare the duration of response (DOR) between treatment arms (Phase 2 Portion)
- To compare progression-free survival (PFS) between treatment arms (Phase 2 Portion)
- To compare the rate of transformation to acute myeloid leukemia (AML) between treatment arms (Phase 2 Portion)
- To compare the overall survival (OS) between treatment arms (Phase 2 Portion)

Exploratory Objectives:

- To assess the pharmacokinetics (PK) and pharmacodynamics of vadastuximab talirine (Phase 1 and Phase 2 Portions)
- To assess the incidence of antitherapeutic antibodies (ATAs) against vadastuximab talirine (Phase 1 and Phase 2 Portions)
- To assess exploratory biomarkers of clinical activity of vadastuximab talirine in combination with azacitidine (Phase 1 and Phase 2 Portions)
- To assess quality of life (QoL; Phase 2 Portion)

STUDY DESIGN AND METHODOLOGY: This is a phase 1/2 study to evaluate the combination of vadastuximab talirine and azacitidine in subjects with previously untreated IPSS Intermediate-2 or High risk MDS. In the Phase 1 Portion of the trial, escalating doses of vadastuximab talirine will be evaluated in combination with azacitidine, and 1 dose will be selected for the randomized, double-blind, placebo-controlled Phase 2 Portion of the study, which is designed to compare the ORR between 2 study arms.

Phase 1 Portion – Open-Label Dose Evaluation

Cohorts of 6 dose-limiting toxicity (DLT)-evaluable subjects will be enrolled in an open-label fashion to receive vadastuximab talirine (intravenous [IV]) push in combination with azacitidine (75 mg/m^2; subcutaneously [SC] or IV) in 28-day cycles, starting at 5 mcg/kg vadastuximab talirine. The DLT-evaluable population will include all Phase 1 subjects who have completed at least Cycle 1 of treatment

(Cycle 1 of treatment is completed when the patient receives the first dose of azacitidine on Day 1 of Cycle 2) *or* discontinued study treatment because of adverse events (AEs), or for a safety-related reason before having had the opportunity to receive the first dose of azacitidine on Day 1 of Cycle 2. In the Phase 1 Portion of the study, DLTs will be defined as posttreatment grade 4 neutropenia or grade 4 thrombocytopenia lasting >42 days from the start of therapy, in the absence of evidence of active MDS, or any grade 3 or higher non-hematologic toxicity that is clearly NOT resulting from underlying MDS or azacitidine, with the exception of:

a. Grade 3 allergic reaction, fatigue, asthenia, anorexia, or constipation
b. Grade 3 nausea, vomiting, or diarrhea not requiring tube feeding or total parenteral nutrition or hospitalization
c. Febrile neutropenia (which resolves with appropriate treatment or marrow recovery), infection, bleeding, or other expected direct complications of cytopenias due to active MDS

If 2 or more subjects in a 6-subject cohort have DLTs, that dose level will be considered to have exceeded the maximum tolerated dose (MTD). If 5 mcg/kg vadastuximab talirine in combination with azacitidine is considered tolerable (≤1 of 6 subjects experiences a DLT), a cohort of 6 DLT-evaluable subjects will receive 10 mcg/kg vadastuximab talirine and azacitidine. If 10 mcg/kg vadastuximab talirine in combination with azacitidine is considered tolerable, a cohort of 6 DLT-evaluable subjects will receive 15 mcg/kg, and if 15 mcg/kg vadastuximab talirine in combination with azacitidine is considered tolerable, a cohort of 6 DLT-evaluable subjects will receive 20 mcg/kg. If 5 mcg/kg vadastuximab talirine in combination with azacitidine is not considered tolerable (>1 of 6 subjects experiences a DLT), a cohort of 6 DLT-evaluable subjects will receive 3 mcg/kg vadastuximab talirine and azacitidine.

Azacitidine will be given 7 times per cycle, either on the first 7 days or 5 days on/2 days off/2 days on; vadastuximab talirine will be given after azacitidine on the last day of azacitidine administration in each cycle. Response assessments (bone marrow examination and complete blood count [CBC]) will be conducted on Day 22-29 of even-numbered cycles until CR, then every 4 cycles thereafter. Subjects may continue on study treatment until disease progression, relapse, or unacceptable toxicity. After discontinuation of study treatment, subjects who have not experienced progression or relapse will continue to be assessed for response every 4 months through 24 months after end of treatment (EOT) or until initiation of another anticancer treatment, progression, or relapse, whichever comes first. All subjects will be contacted for survival status every 2 months after EOT in follow-up until death or study closure, whichever comes first. Safety will be monitored through the surveillance of AEs, laboratory test measures, physical examination findings, and concomitant medication records. An additional bone marrow examination will be conducted for research purposes for subjects in the Phase 1 Portion of the study only.

After 6 DLT-evaluable subjects have had the opportunity to complete at least Cycle 1 (Cycle 1 of treatment is completed when the patient receives the first dose of azacitidine on Day 1 of Cycle 2) of treatment in each planned dose cohort, the data will be aggregated and analyzed by a Safety Monitoring Committee (SMC). Based on the evaluation of the data, including the incidence of DLT in each cohort, the SMC may recommend the dose of vadastuximab talirine for the Phase 2 Portion of the study at the time of the evaluation. If additional safety information is required to recommend a phase 2 dose, the SMC could recommend enrollment of up to 12 additional treated subjects to continue to evaluate the safety of the combination at vadastuximab talirine dose(s) of 3, 5, 10, or 20 mcg/kg. Subsequently, upon completion of dose escalation, up to 12 more expansion patients may be enrolled (maximum of 24 expansion patients total), at any dose level not previously shown to exceed the MTD, to further characterize safety, PK, and activity.

Phase 2 Portion – Randomized, Placebo-Controlled

Subjects will be randomized in a 1:1 manner to one of the study arms described in the following table. Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance score (0 vs 1 or 2) and IPSS score (Intermediate-2 vs High risk).

Study Treatment		Treatment Arm	
		Experimental	Comparator
Open-Label Study Treatment	Azacitidine 75 mg/m^2 SC or IV for 7 days	X	X
Blinded Study Treatment	Vadastuximab talirine (SGN-CD33A) every 4 weeks (after azacitidine on the last day of azacitidine administration) via IV push at SMC-recommended dose	X	
	Placebo every 4 weeks (after azacitidine on the last day of azacitidine administration) via IV push		X

Response assessments (bone marrow examination and CBC) will be conducted once between Day 22 and Day 29 of even-numbered cycles until CR, then every 4 cycles thereafter. Subjects may continue on study treatment until disease progression, relapse, or unacceptable toxicity. After discontinuation of study treatment, subjects who have not experienced progression or relapse will continue to be assessed for response every 4 months through 24 months after EOT or until initiation of another anticancer treatment, progression, or relapse, whichever comes first. All subjects will be contacted for survival status every 2 months after EOT in follow-up until death or study closure, whichever comes first. Safety will be monitored through the surveillance of AEs, laboratory test measures, physical examination findings, and concomitant medication records. An Independent Data Monitoring Committee (IDMC) will also periodically assess the ongoing safety data and make recommendations to either continue evaluating the combination or to stop the study due to toxicity concerns.

STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Subjects cannot be enrolled before all inclusion criteria (including test results) are confirmed.

Inclusion Criteria:

Eligible subjects must meet the following criteria:

1. Subjects with cytologically/histologically confirmed MDS according to the World Health Organization (WHO) 2008 classification, that is determined to be Intermediate-2 (1.5-2 points) or High risk (≥2.5 points) according to the IPSS risk category, with ≥5% and <20% bone marrow blasts.
2. Previously untreated for MDS with the exception of transfusions, hematopoietic growth factors, or immunosuppressive therapy (IST).
3. Age ≥18 years.
4. Subject is eligible for therapy with azacitidine.
5. Life expectancy of at least 12 weeks.
6. ECOG performance status ≤2.
7. The following baseline laboratory data:
   a. white blood cell (WBC) count <20,000/mcL; pre-study use of hydroxyurea to control WBC is acceptable up to 24 hours prior to first dose of study treatment.
   b. direct bilirubin ≤2 x upper limit of normal (ULN) and/or total serum bilirubin ≤1.5 x ULN (or total serum bilirubin ≤3 x ULN for subjects with Gilbert's disease).
   c. serum creatinine ≤2.5 x ULN and creatinine clearance ≥30 mL/min.
   d. alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN.
8. 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 study treatment. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.
9. Females of childbearing potential and males who have partners of childbearing potential must agree to use 2 effective contraception methods during the study and for 6 months following the last dose of study drug.
   Acceptable methods of contraception include: hormonal (birth control pills, injections, implants), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), vasectomy (for males),

barrier methods (male and female condoms, diaphragms, and spermicides), and complete abstinence. Complete abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

10. Subjects must provide written informed consent.

Exclusion Criteria:

If any of the following apply, the subject MUST NOT enter the study:

1. Received prior treatment for MDS with lenalidomide or hypomethylating agents (HMAs).
2. History of one of the following myeloproliferative neoplasms: essential thrombocythemia, polycythemia vera, and primary myelofibrosis.
3. Second malignancy currently requiring active therapy (except for hormonal/anti-hormonal treatment, eg, prostate or breast cancer).
4. Central nervous system leukemia based on imaging or documented positive cytology in cerebral spinal fluid.
5. Any uncontrolled grade 3 or higher (per National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03) viral, bacterial, or fungal infection within 14 days prior to the first dose of study treatment. Antimicrobial prophylaxis or ongoing treatment of resolving/controlled infection is permitted.
6. Known to be positive for hepatitis B by surface antigen expression. Known to have active hepatitis C infection (positive by polymerase chain reaction or on antiviral therapy for hepatitis C within the last 6 months).
7. Known to be positive for human immunodeficiency virus (HIV).
8. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, or myocardial infarction within 6 months prior to their first dose of study drug, or refractory congestive heart failure unresponsive to medical treatment.
9. Therapy with the following agents within the specified timeframe prior to first study treatment:
    a. systemic anti-neoplastic or investigational agents within prior 14 days.
    b. hematopoietic growth factors within 7 days (erythropoietin, granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor, or thrombopoietin receptor agonists).
10. Known hypersensitivity to any excipient contained in the drug formulation of any study treatment.
11. Prior allogeneic hematopoietic stem cell transplant, for any indication.
12. Hypocellular MDS, defined as bone marrow cellularity <30% in subjects ≤60 years old or <20% cellularity in subjects >60 years old.
13. Candidates for allogeneic stem cell transplant at the time of screening.
14. History of clinically significant liver disease (e.g. liver cirrhosis) or ongoing alcohol abuse.

NUMBER OF SUBJECTS: Approximately 142 subjects; up to 36 in phase 1 and approximately 106 in phase 2

STUDY TREATMENT(S):

Test Product, Dose and Mode of Administration:

Phase 1 Portion:

Vadastuximab talirine (SGN-CD33A) every 4 weeks (after azacitidine on the last day of azacitidine administration) via IV push at 5 mcg/kg up to 20 mcg/kg (with possible de-escalation to 3 mcg/kg), based on the dose escalation.

Azacitidine 75 mg/m^2 SC or IV for 7 days (7 consecutive days or 5 days on/2 days off/2 days on), beginning on Day 1 of repeated 4-week cycles.

Phase 2 Portion:

Vadastuximab talirine or placebo every 4 weeks (after azacitidine on the last day of azacitidine administration) via IV push at the dose determined in the Phase 1 Portion.

Azacitidine 75 mg/m^2 SC or IV (at the Investigator's discretion) for 7 days (7 consecutive days or 5 days on/ 2 days off/2 days on), in repeated 4-week cycles.

Reference Therapy, Dose and Mode of Administration:

Inactive placebo matching vadastuximab talirine will be provided for the Phase 2 Portion.

DURATION OF TREATMENT: Study treatment consists of repeated 4-week cycles of combination treatment. Subjects may continue on study treatment until disease progression, relapse, or unacceptable toxicity, whichever comes first.

STUDY EVALUATIONS:

Efficacy Evaluations:

Activity will be assessed by routine laboratory tests (blood counts) and bone marrow examinations. Response categorization will be based on the International Working Group (IWG) Response Criteria in Myelodysplasia (Cheson 2006).

Primary Efficacy Criteria:

Overall response rate (ORR), defined as the proportion of subjects who achieve any category of CR (CR includes CR and Marrow CR) or PR based on the 2006 IWG criteria for MDS.

Secondary Efficacy Criteria:

Secondary efficacy endpoints include the following:

- Complete response (CR) rate
- Hematologic improvement (HI) rate
- Duration of response (DOR)
- Progression-free survival (PFS)
- Rate of transformation to AML
- Overall survival (OS)

Pharmacokinetic (PK) and Antitherapeutic Antibody (ATA) Assessments:

Blood samples for PK and ATA assessment will be collected at baseline and throughout the treatment period. Sensitive, qualified assays will be used to measure concentrations of antibody-drug conjugate (ADC; vadastuximab talirine) and SGD-1882 in plasma and ATAs in serum. The remaining PK samples will be archived for possible analysis of vadastuximab talirine-related species. The assays will include enzyme-linked immunosorbent assays (ELISA) and liquid chromatography/tandem mass spectrometry assays, as well as other assays if further characterization is required. A qualified electrochemiluminescence assay will be used to assess ATA.

Biomarker Assessments:

Peripheral blood and bone marrow aspirates will be collected at baseline and throughout the treatment period. Biomarker assessments may include CD33 expression level, abundance of myeloid-derived suppressor cells (MDSC), characterization of leukocyte subpopulations in peripheral blood, variation in sequence of CD33 and genes commonly mutated in MDS and hematologic malignancies, soluble CD33, abundance of a variety of cytokines, and testing for Paroxysmal Nocturnal Hemoglobinuria (PNH) and human leukocyte antigen (HLA)-DR15 at protocol-specified time points. Methods of analysis may include flow cytometry, ELISA, and DNA and RNA sequencing.

Safety Criteria:

Safety assessments will consist of the surveillance of AEs, laboratory test measures, physical examination findings, and concomitant medication records.

Quality of Life (QoL):

Quality of life will be assessed with the patient reported outcomes (PRO) tool Quality of Life Questionnaire (QLQ)-C30 at protocol-defined time points.

STATISTICAL METHODS:

Stratification (Phase 2 Portion only)

Subjects will be stratified by baseline ECOG performance score (0 vs 1 or 2) and IPSS risk category (Intermediate-2 vs High risk).

Sample Size Considerations

Phase 1 Portion (minimum of 6 subjects per cohort): Six subjects are adequate to appropriately assess the safety profiles and DLT rates of differing dose levels of vadastuximab talirine in combination with azacitidine. If the true incidence rate of DLT is 10%, the probability of considering a dose level tolerable (ie, ≤1 of 6 subjects experiences a DLT) will be 88.6%. If the true incidence rate of DLT is 50%, the probability of considering a dose level tolerable will be 10.9%.

Phase 2 Portion (106 subjects): A sample size of 106 subjects will provide 85% power to detect a treatment difference in ORR, assuming an ORR of 30% for azacitidine alone vs 55% for the combination of vadastuximab talirine with azacitidine, at a 2-sided 0.1 alpha level.

Analysis Methods

The primary efficacy endpoint of the study is ORR in the Phase 2 Portion, defined as the proportion of subjects who achieve any category of CR (CR and Marrow CR) or PR based on the 2006 IWG criteria for MDS. Subjects who receive other MDS therapies before a response has been observed will be considered non-responders. The ORR will be summarized by treatment group and the corresponding 90% confidence intervals will be calculated. The treatment difference in ORR will be tested using a Cochran-Mantel-Haenszel test.

Secondary efficacy endpoints include CR rate, HI rate, DOR, PFS, rate of transformation to AML, and OS. Treatment differences in the rate of CR, HI, and transformation to AML will be analyzed by the same method as for ORR. DOR, PFS, and OS will be estimated with the Kaplan-Meier method and tested with the stratified log-rank test.

The primary analysis of efficacy will be based on the intent-to-treat (ITT) analysis set, which includes all subjects who are randomized in the Phase 2 Portion of the study.

Descriptive summaries of subject disposition, demographics, disease characteristics, baseline and pharmacodynamics biomarkers, extent of exposure to study treatment, and safety will be provided. The relationship of vadastuximab talirine PK and relevant pharmacodynamic endpoints, safety, or efficacy may be explored; these analyses, if conducted, will be descriptive.

DATE AND VERSION: 13 April 2017, Version 03

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
ADC	Antibody-drug conjugate
AE	Adverse event
Allo-HCT	Allogeneic hematopoietic stem cell transplant
ALT	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
AML	Acute myeloid leukemia
ANA	Antinuclear antibodies
ANC	Absolute neutrophil count
ANCA	Anti-neutrophil cytoplasmic antibodies
anti-dsDNA	Anti-double-stranded DNA
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
ATA	Antitherapeutic antibody
CBC	Complete blood count
CFR	Code of Federal Regulations
CR	Complete response
CRO	Clinical research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assays
EOT	End of treatment
FAB	French-American-British
FDA	Food and Drug Administration
GCP	Good Clinical Practice
β-hCG	Beta human chorionic gonadotropin
HI	Hematologic improvement
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMA	Hypomethylating agent
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee

Ig	Immunoglobulin
IND	Investigational New Drug
INN	International Nonproprietary Name
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IST	Immunosuppressive therapy
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous(ly)
IWG	International Working Group
IXRS	Interactive voice and web recognition system
LDH	Lactate dehydrogenase
MDS	Myelodysplastic syndromes
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PBD	Pyrrolobenzodiazepine
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PFS	Progression-free survival
PICC	Peripherally-inserted central catheter
PK	Pharmacokinetic(s)
PNH	Paroxysmal Nocturnal Hemoglobinuria
PR	Partial response
PRO	Patient reported outcomes
QLQ	Quality of Life Questionnaire
QoL	Quality of life
RA	Refractory anemia
RAEB	Refractory anemia with excess blasts
RAEB-T	Refractory anemia with excess blasts in transformation
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical analysis plan

SC	Subcutaneous(ly)
SD	Stable disease
SMC	Safety Monitoring Committee
SMPC	Summary of product characteristics
SOP	Standard Operating Procedure
SOS/VOD	Sinusoidal obstruction syndrome/veno-occlusive disease
Study drug	Azacitidine with or without vadastuximab talirine
TEAE	Treatment-emergent AE
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
USPI	United States prescribing information
WBC	White blood cell
WFI	Water for Injection
WHO	World Health Organization

5. ETHICS

5.1 Ethics Committee

This study will be conducted in compliance with Institutional Review Board (IRB) and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines - including Title 21 Part 56 of the United States (US) Code of Federal Regulations (CFR) relating to IRBs and GCP as described in the US Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312) - in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B[R3]), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH regulations regarding scientific integrity (E4, E8, E9, and E10). In addition this study will adhere to all local regulatory requirements and requirements for data protection.

Before initiating a trial/study, the Investigator/institution must have written and dated approval/favorable opinion from the IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject recruitment procedures (eg, advertisements), and any written information to be provided to subjects and a statement from the IRB that they comply with GCP requirements. The IRB approval must identify the protocol version as well as the documents reviewed.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonized Tripartite Guideline E6 (R1); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Fortaleza, Brazil, October 2013; Appendix 18.1), and all applicable regulatory requirements.

5.3 Subject Information and Consent

The Investigator will explain the benefits and risks of participation in the study to each subject and obtain written informed consent. Written informed consent must be obtained prior to the subject entering the study and before initiation of any study-related procedure (including administration of study drug).

The Sponsor will provide a sample informed consent form, based on the elements of informed consent in Appendix 18.2. The final, version dated form must be agreed to by the Sponsor and the IRB and will contain all elements in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed informed consent.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject. In this instance approval should always be given by the IRB. Subjects on treatment should be informed of the changes and reconsented if the consent was updated for safety reasons. This is documented in the same way as previously described.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study will be performed at approximately 35 sites in North America.

Monitoring and Evaluation Committee(s):

The Phase 1 Portion of this study is an open-label, dose-escalation study. Safety will be monitored through the surveillance of adverse events (AEs), laboratory test measures, physical examination findings, and concomitant medication records and will be monitored in an ongoing process as part of the dose-escalation portion of this study by a Safety Monitoring Committee (SMC). During the Phase 2 Portion, an Independent Data Monitoring Committee (IDMC) will also periodically assess the ongoing safety data and make recommendations to either continue evaluating the combination or to stop the study due to toxicity concerns. Conditions requiring IDMC action are provided in Section 13.6.10.

Clinical Laboratories:

Central clinical laboratory services will be provided by a central laboratory (refer to the study manual) for protocol-required hematology and serum chemistry tests; central laboratory results will not be provided to the Investigator. Additional analyses of clinical laboratory samples may be conducted by certified local laboratories. Documentation of certification will be filed with study documentation.

Analyses of antibody-drug conjugate (ADC; vadastuximab talirine) and SGD-1882 concentrations and other research studies will be performed at central facilities that will be identified in the study manual.

Clinical Research Organization (CRO):

PRA Health Sciences
4130 ParkLake Avenue, Suite 400
Raleigh, NC 27612 US

Medical Monitor/Medical Expert:

7. INTRODUCTION

7.1 Disease Review

The myelodysplastic syndromes (MDS) represent a group of heterogeneous hematopoietic disorders derived from an abnormal multipotent progenitor cell. They are characterized by ineffective hematopoiesis, bone marrow failure, peripheral blood cytopenias, and reduced survival. MDS may be classified as indolent or aggressive (lower- or higher-risk), depending on life expectancy and likelihood of progression to acute myeloid leukemia (AML). The annual age-adjusted incidence of MDS is approximately 4.5 per 100,000 in the US. MDS is associated with age, and the incidence of MDS for Americans ≥50 years of age is approximately 15.5 per 100,000 per year. [1]

Prognosis in MDS depends on the number of bone marrow blasts, cytogenetic abnormalities, and the amount of peripheral blood cytopenias. These risk factors are scored in the International Prognostic Scoring System (IPSS) as percent bone marrow blasts (<5% =0, 5%-10% =0.5, and 11%-20% =1.5), karyotype (good [normal, -Y, del(5q), del(20q)] =0; intermediate [other abnormalities] =0.5, and poor [≥3 abnormalities] =1.0), and cytopenias (0 or 1 =0 and 2 or 3 =0.5). Patients are assigned scores based on the sum of risk factor scores, and prognosis is defined as Low (score =0), Intermediate-1 (score =0.5-1.0), Intermediate-2 (score =1.5-2.0), and High (score ≥2.5) risk. These scores have been shown to predict survival and risk of progression to AML. [2; Appendix 18.5.1] MDS can also be classified according to the World Health Organization (WHO) system using morphologic, cytochemical, and immunophenotypic features of the neoplastic cells, [Appendix 18.5.2] an update to the older French-American-British (FAB) classification.

For patients with Low or Intermediate-1 risk MDS, standard treatment is usually supportive care; symptomatic anemia is treated with growth factors as appropriate (patients with del(5q) and symptomatic anemia are generally treated with lenalidomide). Among patients who are intolerant or fail to respond to treatment with erythropoiesis-stimulating agents, those with low serum erythropoietin levels (<500 mU/mL) may be candidates for immunosuppressive therapy (IST) with antithymocyte globulin/cyclosporine. Those not candidates for IST and those who are intolerant of or fail to respond to IST are generally treated with hypomethylating agents (HMAs; azacitidine or decitabine); HMA treatment generally continues for at least 4-6 cycles with maintenance treatment until disease progression. [3]

For patients with Intermediate-2 or High risk MDS, allogeneic hematopoietic stem cell transplant (allo-HCT) is the preferred treatment for patients who are candidates and have a donor stem cell source available. However, the majority of higher-risk MDS patients are not eligible for allo-HCT due to age, comorbidities, or donor availability. For such patients who are not candidates for allo-HCT, treatment with HMAs as described above is appropriate. In this setting, azacitidine is the preferred agent, as only azacitidine has demonstrated an improvement in overall survival (OS) when compared to standard of care in a randomized controlled trial. [4] There is no standard treatment for patients who do not respond to or relapse following HMA treatment. [3]

CD33 is an important cell-surface marker that is found on cells committed to the myeloid lineage, myeloid leukemic blasts, and mature monocytes, but not on normal pluripotent hematopoietic stem cells. [5, 6] CD33 has been used to diagnose AML, [7] and anti-CD33 antibodies have been investigated as therapy in AML. [8, 9] Though lasting clinical benefit has not been demonstrated with gemtuzumab ozogamicin, CD33 continues to be a target of interest in AML. [9, 10] In MDS, CD33 is also highly expressed in myeloid blast cells, as well as myeloid-derived suppressor cells (MDSC), which have been shown to mediate myelodysplasia via suppressive cytokine production and enhanced apoptosis. [6, 11, 12]

7.2 Compound Review

Vadastuximab talirine (also referred to as SGN-CD33A or 33A) is an ADC composed of an antibody (h2H12ec) conjugated to a DNA-cross linking pyrrolobenzodiazepine (PBD) dimer drug (SGD-1882) via a protease-cleavable linker. The antibody targets the antigen CD33, which is expressed on leukemic cells of myeloid origin such as on AML, chronic myeloid leukemia, and MDS cells. In nonclinical studies, vadastuximab talirine was active in animal models of AML, including in multidrug-resistant lineages. [13]

There are 2 ongoing clinical studies with vadastuximab talirine. The first-in-human phase 1 clinical trial (Study SGN33A-001) is a dose-escalation study to evaluate the safety and tolerability of vadastuximab talirine in subjects with CD33-positive AML. Dosing began at 5 mcg/kg on Day 1 (in repeated 3-week cycles) and has been escalated to 60 mcg/kg. An additional arm was added to study vadastuximab talirine in combination with HMAs in subjects with CD33-positive AML, which began dosing at 10 mcg/kg (in repeated 4-week cycles). As of this writing, 86 subjects with AML had received monotherapy and 21 subjects had received vadastuximab talirine plus HMA combination therapy in Study SGN33A-001. The most common AEs in the monotherapy cohorts were febrile neutropenia (70%), fatigue (45%), anemia (26%), decreased appetite (26%), dyspnea (26%), thrombocytopenia (24%), constipation (23%), nausea (23%), cough (22%), diarrhea (22%), and peripheral edema (21%). The most common AEs observed in the combination cohort of SGN33A-001 were fatigue (38%), febrile neutropenia (38%), constipation (19%), and nausea (19%). [14]

The phase 1b clinical trial (Study SGN33A-002) is a dose-escalation study to evaluate the safety and tolerability of vadastuximab talirine in combination with standard induction and consolidation therapy and as maintenance monotherapy in subjects with newly diagnosed AML. Study SGN33A-002 began dosing at 10 mcg/kg for induction (Days 1 and 4) and consolidation (Day 1 of 28-day cycles for up to 4 cycles), and 5 mcg/kg for maintenance (Day 1 of 6-week cycles). As of this writing, 7 subjects with AML had enrolled in Study SGN33A-002. Adverse events observed in SGN33A-002 were febrile neutropenia, headache, hyperglycemia, and stomatitis (1 subject each). Additional clinical data are presented in the Investigator's Brochure. [14]

Azacitidine (VIDAZA®) is a nucleoside metabolic inhibitor that is indicated for the treatment of subjects with certain FAB MDS subtypes. [15] Azacitidine is a pyrimidine nucleoside analog of cytidine. It is believed to exert its anti-neoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. Azacitidine is indicated for refractory anemia (RA) or RA with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), RA with excess blasts (RAEB), RA with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia MDS subtypes. Azacitidine is administered at a dose of 75 mg/m^2 subcutaneously (SC) or intravenously (IV), daily for 7 days every 28 days. [15] At some institutions, azacitidine is administered on a 5 days on/2 days off/2 days on schedule, rather than for 7 consecutive days. [3, 16 – 18]

7.3 Clinical Study Rationale

Though HMAs are part of the standard treatment protocols for MDS, the benefits are limited. In subjects with Intermediate-2 or High risk MDS, median OS with azacitidine was 21 to 24 months. [19, 20] Decitabine has been shown to produce durable responses, but an improvement in OS has not been demonstrated. [21] Improved treatment options are needed for Intermediate-2 and High risk MDS, particularly for subjects not eligible for allo-HCT. By targeting CD33, combining vadastuximab talirine with azacitidine may add significant activity in allo-HCT-ineligible subjects compared to treatment with azacitidine alone. Vadastuximab talirine (10 mcg/kg) has been administered with azacitidine at standard doses (75 mg/m^2 per day for 7 consecutive days) to subjects with AML without unacceptable toxicity in Study SGN33A-001, suggesting that the combination may also have an acceptable safety profile in subjects with MDS.

The study will assess the safety of vadastuximab talirine in combination with azacitidine in a dose-escalation Phase 1 Portion of the study and its efficacy in a double-blind Phase 2 Portion at the dose identified in phase 1. The safety of this drug combination will be monitored in an ongoing process as part of the dose-escalation portion of this study by an SMC, and safety and toxicity will be monitored during the double-blind portion by an IDMC.

8. STUDY OBJECTIVES

8.1 Primary Study Objective

8.1.1 Phase 1 Portion

- To determine the recommended vadastuximab talirine (SGN-CD33A) dose in combination with azacitidine.

8.1.2 Phase 2 Portion

- To compare the overall response rate (ORR = complete response + partial response [CR+PR]) between treatment arms.

8.2 Secondary Study Objectives

- To evaluate the safety of the combination of vadastuximab talirine and azacitidine (Phase 1 and Phase 2 Portions)
- To compare the CR rate between treatment arms (Phase 2 Portion)
- To compare the hematologic improvement (HI) rate between treatment arms (Phase 2 Portion)
- To compare the duration of response (DOR) between treatment arms (Phase 2 Portion)
- To compare progression-free survival (PFS) between treatment arms (Phase 2 Portion)
- To compare the rate of transformation to AML between treatment arms (Phase 2 Portion)
- To compare the OS between treatment arms (Phase 2 Portion)

8.3 Exploratory Objectives

- To assess the pharmacokinetics (PK) and pharmacodynamics of vadastuximab talirine (Phase 1 and Phase 2 Portions)
- To assess the incidence of antitherapeutic antibodies (ATAs) against vadastuximab talirine (Phase 1 and Phase 2 Portions)
- To assess exploratory biomarkers of clinical activity of vadastuximab talirine in combination with azacitidine (Phase 1 and Phase 2 Portions)
- To assess quality of life (QoL; Phase 2 Portion)

8.4 Endpoints

8.4.1 Primary Endpoint

The primary endpoint of the Phase 1 Portion of the study is to determine the recommended dose for the Phase 2 Portion, based upon the maximum tolerated dose (MTD).

The primary efficacy endpoint of the Phase 2 Portion of the study is the ORR, defined as the proportion of subjects who achieve any category of CR (CR and Marrow CR) or PR based on the 2006 International Working Group (IWG) criteria for MDS. [22]

8.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints of the Phase 2 Portion of the study are the following:

- CR rate
- HI rate
- DOR
- PFS
- Rate of transformation to AML
- OS

8.4.3 Pharmacokinetic and Antitherapeutic Antibody Assessments

- Estimates of selected PK parameters for plasma vadastuximab talirine and released SGD-1882
- Incidence of ATA

8.4.4 Biomarker Assessments

Biomarker assessments may include

- CD33 expression level
- Abundance of MDSC
- Characterization of leukocyte subpopulations in peripheral blood (peripheral blood mononuclear cells; PBMCs)
- Variation in sequence of CD33 and genes commonly mutated in MDS and hematologic malignancies

- Soluble CD33
- Abundance of a variety of cytokines
- Testing for Paroxysmal Nocturnal Hemoglobinuria (PNH) and human leukocyte antigen (HLA)-DR15

8.4.5 Safety Criteria

Safety assessments will consist of the surveillance of AEs, laboratory test measures, physical examination findings, and concomitant medication records.

8.4.6 Quality of Life

Quality of life will be assessed with the Quality of Life Questionnaire (QLQ)-C30 patient reported outcomes (PRO) tool at protocol-defined time points.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a phase 1/2 study to evaluate the combination of vadastuximab talirine (SGN-CD33A) and azacitidine in subjects with previously untreated IPSS Intermediate-2 or High risk MDS. In the Phase 1 Portion of the trial, escalating doses of vadastuximab talirine will be evaluated in combination with azacitidine, and 1 dose will be selected for the randomized, double-blind, placebo-controlled Phase 2 Portion of the study, which is designed to compare the ORR between the 2 study arms.

9.1.1 Phase 1 Portion – Open-Label Dose Evaluation

Cohorts of 6 dose-limiting toxicity (DLT)-evaluable subjects will be enrolled in an open-label fashion to receive vadastuximab talirine in combination with azacitidine in 28-day cycles, starting at 5 mcg/kg vadastuximab talirine. The DLT-evaluable population will include all Phase 1 subjects who have completed at least Cycle 1 of treatment (Cycle 1 of treatment is completed when the patient receives the first dose of azacitidine on Day 1 of Cycle 2) *or* discontinued study treatment because of AEs, or for a safety-related reason before having had the opportunity to receive the first dose of azacitidine on Day 1 of Cycle 2. In the Phase 1 Portion of the study, DLTs will be defined as posttreatment grade 4 neutropenia or grade 4 thrombocytopenia lasting >42 days from the start of therapy, in the absence of evidence of active MDS, or any grade 3 or higher non-hematologic toxicity that is clearly NOT resulting from underlying MDS or azacitidine, with the exception of:

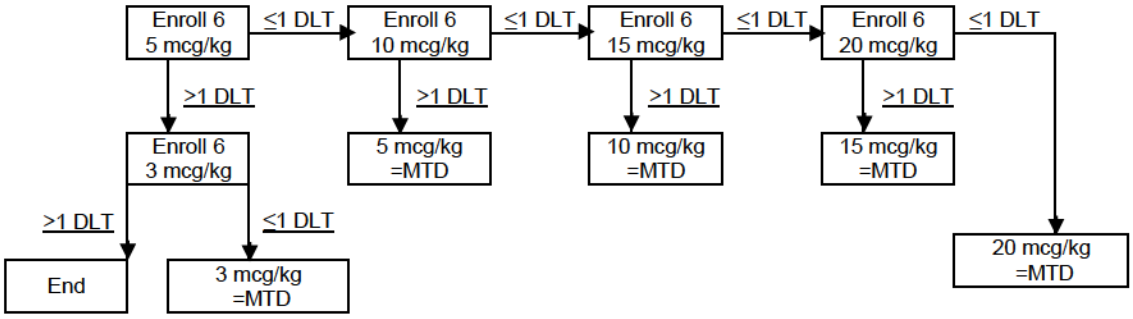
a. Grade 3 allergic reaction, fatigue, asthenia, anorexia, or constipation

b. Grade 3 nausea, vomiting, or diarrhea not requiring tube feeding or total parenteral nutrition or hospitalization

c. Febrile neutropenia (which resolves with appropriate treatment or marrow recovery), infection, bleeding, or other expected direct complications of cytopenias due to active MDS

If 2 or more subjects in a 6-subject cohort have DLTs, that dose level will be considered to have exceeded the MTD. If 5 mcg/kg vadastuximab talirine in combination with azacitidine is considered tolerable (≤1 of 6 subjects experiences a DLT), a cohort of 6 DLT-evaluable subjects will receive 10 mcg/kg vadastuximab talirine and azacitidine. If 10 mcg/kg vadastuximab talirine in combination with azacitidine is considered tolerable, a cohort of 6 DLT-evaluable subjects will receive 15 mcg/kg, and if 15 mcg/kg vadastuximab talirine in combination with azacitidine is considered tolerable, a cohort of 6 DLT-evaluable subjects will receive 20 mcg/kg. If 5 mcg/kg vadastuximab talirine in combination with azacitidine is not considered tolerable (>1 of 6 subjects experiences a DLT), a cohort of 6 DLT-evaluable subjects will receive 3 mcg/kg vadastuximab talirine and azacitidine. The dose-escalation plan is presented in Figure 1.

Figure 1: Study Schematic – Phase 1 Portion



DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

Azacitidine will be given on 7 days per cycle, either on the first 7 days or 5 days on/2 days off/2 days on; vadastuximab talirine will be given after azacitidine on the last day of azacitidine administration in each cycle. Response assessments (bone marrow examination and complete blood count [CBC]) will be conducted on Day 22-29 of even-numbered cycles until CR, then every 4 cycles thereafter. Subjects may continue on study treatment until disease progression, relapse, or unacceptable toxicity. After discontinuation of study treatment, subjects who have not experienced progression or relapse will continue to be assessed for response every 4 months through 24 months after the end of treatment (EOT) or until initiation of another anticancer treatment, progression, or relapse, whichever comes first. All subjects will be contacted for survival status every 2 months after EOT in follow-up until death or study closure, whichever comes first. Safety will be monitored through the surveillance of AEs, laboratory test measures, physical examination findings, and concomitant medication records. An additional bone marrow examination will be conducted for research purposes for subjects in the Phase 1 Portion of the study only.

After 6 DLT-evaluable subjects have had the opportunity to complete at least Cycle 1 (Cycle 1 of treatment is completed when the patient receives the first dose of azacitidine on Day 1 of Cycle 2) of treatment in each planned dose cohort, the data will be aggregated and analyzed by an SMC (Section 13.6.9). Based on the evaluation of the data, including the incidence of DLT in each cohort, the SMC may recommend the dose of vadastuximab talirine for the Phase 2 Portion of the study at the time of the evaluation. If additional safety information is required to recommend a phase 2 dose, the SMC could recommend enrollment of up to 12 additional treated subjects to continue to evaluate the safety of the combination at vadastuximab talirine dose(s) of 3, 5, 10, or 20 mcg/kg. Subsequently, upon completion of dose escalation, up to 12 more expansion patients may be enrolled (maximum of 24 expansion patients total), at any dose level not previously shown to exceed the MTD, to further characterize safety, PK, and activity.

9.1.2 Phase 2 Portion – Randomized, Placebo-Controlled

Subjects will be randomized in a 1:1 manner to one of the study arms described in Table 1. Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1 or 2) and IPSS score (Intermediate-2 vs High risk).

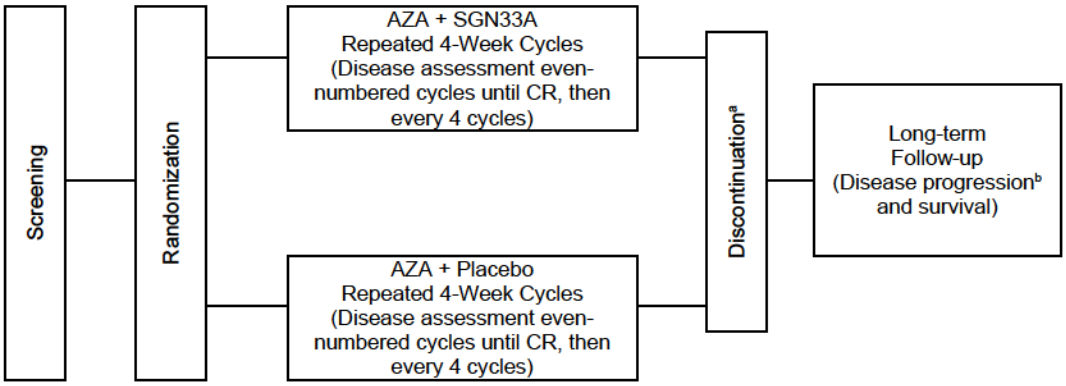
Table 1: Treatment Arms

Study Treatment		Treatment Arm	
		Experimental	Comparator
Open-Label Study Treatment	Azacitidine 75 mg/m^2 SC or IV (at the Investigator's discretion) for 7 days	X	X
Blinded Study Treatment	Vadastuximab talirine (SGN-CD33A) every 4 weeks (after azacitidine on the last day of azacitidine administration) via IV push at SMC-recommended dose	X	
	Placebo every 4 weeks (after azacitidine on the last day of azacitidine administration) via IV push		X

IV = intravenous; SC = subcutaneous; SMC = Safety Monitoring Committee.

Subjects will receive vadastuximab talirine in combination with azacitidine in 28-day cycles, starting at the dose level of vadastuximab talirine determined in phase 1. Response assessments (bone marrow examination and CBC) will be conducted once between Day 22 and Day 29 of even-numbered cycles until CR, then every 4 cycles thereafter. Subjects may continue on study treatment until disease progression, relapse, or unacceptable toxicity. After discontinuation of study treatment, subjects who have not had progression or relapse will continue to be assessed for response every 4 months through 24 months after EOT or until initiation of another anticancer treatment, progression, or relapse, whichever comes first. All subjects will be contacted for survival status every 2 months after EOT in follow-up until death or study closure, whichever comes first. Safety will be monitored through the surveillance of AEs, laboratory test measures, physical examination findings, and concomitant medication records. An IDMC (Section 13.6.10) will also periodically assess the ongoing safety data and make recommendations to either continue evaluating the combination or to stop the study due to toxicity concerns. Figure 2 is a study schematic for the Phase 2 Portion.

Figure 2: Study Schematic – Phase 2 Portion



AZA = azacitidine; CR = complete response.

a Subjects may continue to receive repeated cycles of treatment until disease progression, relapse, unacceptable toxicity, or other discontinuation criteria are met.

b For subjects who discontinue without having experienced disease progression follow-up will include disease assessment (CBC and bone marrow) every 4 months for 24 months or until disease progression. Subjects will be followed every 2 months for survival until death or the end of the study.

Unblinding a subject's treatment assignment will be limited to emergency circumstances where knowledge of the treatment assignment would affect decisions regarding the management of the subject. In the event of such an emergency circumstance, a formal unblinding procedure will be followed to allow the Investigator to immediately access a

subject's treatment assignment. Information on study treatment assignment should not be distributed to any other personnel involved in the clinical trial.

9.1.3 Study Stopping Criteria

The SMC (Phase 1 Portion) or the IDMC (Phase 2 Portion) will provide recommendations to the Sponsor if either of the following criteria are met:

- [redacted]
- [redacted]

The Sponsor will pause enrollment and notify the FDA and other health authorities, as applicable, if the stopping criteria are met.

9.2 Discussion of Study Design

The Phase 1 Portion of this study is a dose-escalation design to balance subject safety and speed of accrual while minimizing the number of subjects exposed to subtherapeutic doses. [23] This is a standard design in clinical oncology development.

The Phase 2 Portion is a randomized, double-blind study. Randomization reduces the risk of bias in treatment allocation, and the double-blind methodology reduces the risk of bias in treatment or assessment.

The safety and efficacy assessments in both portions are standard and well accepted measures in clinical oncology.

9.3 Study Duration

Study treatment consists of repeated 4-week cycles of combination treatment. Subjects may continue to receive treatment until they experience disease progression, relapse, or unacceptable toxicity.

The estimated duration of study treatment through final primary analysis is approximately 51 months from enrollment of the first subject to completion of the last subject. All subjects will be contacted for survival status every 2 months after EOT in follow-up until death or study closure, whichever comes first.

9.4 Study Population

9.4.1 Inclusion Criteria

Subjects cannot be enrolled before all inclusion criteria (including test results) are confirmed.

Eligible subjects must meet the following criteria:

1. Subjects with cytologically/histologically confirmed MDS according to the WHO 2008 classification, that is determined to be Intermediate-2 (1.5-2-points) or High risk (≥2.5 points) according to the IPSS risk category, with ≥5% and <20% bone marrow blasts.

2. Previously untreated for MDS with the exception of transfusions, hematopoietic growth factors, or IST.

3. Age ≥18 years.

4. Eligible for therapy with azacitidine.

5. Life expectancy of at least 12 weeks.

6. ECOG performance status ≤2.

7. The following baseline laboratory data:

    a. white blood cell (WBC) count <20,000/mcL; pre-study use of hydroxyurea to control WBC is acceptable up to 24 hours prior to first dose of study treatment.

    b. direct bilirubin ≤2 x upper limit of normal (ULN) and/or total serum bilirubin ≤1.5 x ULN (or total serum bilirubin ≤3 x ULN for subjects with Gilbert's disease).

    c. serum creatinine ≤2.5 x ULN and creatinine clearance ≥30 mL/min (calculated using the Cockcroft-Gault formula; Section 11.7).

    d. alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN.

8. 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 study treatment. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.

9. Females of childbearing potential and males who have partners of childbearing potential must agree to use 2 effective contraception methods during the study and for 6 months following the last dose of study drug.

Acceptable methods of contraception include: hormonal (birth control pills, injections, implants), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), vasectomy (for males), barrier methods (male and female condoms, diaphragms, and spermicides), and complete abstinence. Complete abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

10. Subjects must provide written informed consent.

9.4.2 Exclusion Criteria

If any of the following apply, the subject **MUST NOT** enter the study:

1. Received prior treatment for MDS with lenalidomide or HMAs.

2. History of one of the following myeloproliferative neoplasms: essential thrombocythemia, polycythemia vera, and primary myelofibrosis.

3. Second malignancy currently requiring active therapy (except for hormonal/anti-hormonal treatment, eg, prostate or breast cancer).

4. Central nervous system leukemia based on imaging or documented positive cytology in cerebral spinal fluid.

5. Any uncontrolled grade 3 or higher (per National Cancer Institute [NCI; US] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03) viral, bacterial, or fungal infection within 14 days prior to the first dose of study treatment. Antimicrobial prophylaxis or ongoing treatment of resolving/controlled infection is permitted.

6. Known to be positive for hepatitis B by surface antigen expression. Known to have active hepatitis C infection (positive by polymerase chain reaction or on antiviral therapy for hepatitis C within the last 6 months).

7. Known to be positive for human immunodeficiency virus (HIV).

8. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, or myocardial infarction within 6 months prior to their first dose of study drug, or refractory congestive heart failure unresponsive to medical treatment.

9. Therapy with the following agents within the specified timeframe prior to first study treatment:

    a. systemic anti-neoplastic or investigational agents within prior 14 days.

b. hematopoietic growth factors within 7 days (erythropoietin, granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor, or thrombopoietin receptor agonists).

10. Known hypersensitivity to any excipient contained in the drug formulation of any study treatment.

11. Prior allo-HCT, for any indication.

12. Hypocellular MDS, defined as bone marrow cellularity <30% in subjects ≤60 years old or <20% cellularity in subjects >60 years old.

13. Candidates for allogeneic stem cell transplant at the time of screening.

14. History of clinically significant liver disease (e.g. liver cirrhosis) or ongoing alcohol abuse.

9.4.3 Withdrawal and Replacement of Subjects

In accordance with the Declaration of Helsinki (Appendix 18.1) and applicable regulations, a subject has the right to discontinue treatment or withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

9.4.3.1 Discontinuation of Study Drug

Subjects may continue on study treatment until disease progression, relapse, or unacceptable toxicity. After discontinuation of study treatment, subjects who have not experienced progression or relapse will continue to be assessed for response every 4 months through 24 months after EOT or until initiation of another anticancer treatment, progression, or relapse, whichever comes first. All subjects will be contacted for survival status every 2 months after EOT in follow-up until death or study closure, whichever comes first.

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

- Progressive disease (PD) or relapse after remission
- AE
- Investigator decision
- Subject decision, non-AE
- Study termination by Sponsor
- Other, non-AE

The reason for treatment discontinuation will be recorded in the clinical records and the electronic Case Report Form (eCRF). All subjects who discontinue treatment will undergo an EOT visit (see Section 10.3). These subjects will continue to be followed for survival and disease status (see Section 10.4) unless they withdraw from the study (see Section 9.4.3.2). For replacement of withdrawn/discontinued subjects, see Section 9.4.3.3.

9.4.3.2 Subject Withdrawal From Study

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

- Subject withdrawal of consent
- Study termination by Sponsor
- Lost to follow-up
- Death
- Other

Subjects who withdraw from the study will not be further contacted.

9.4.3.3 Replacement of Subjects

During the Phase 1 Portion, sufficient DLT-evaluable subjects will be enrolled in each cohort for determination of the DLT (6 DLT-evaluable subjects per cohort in the absence of DLTs). During the Phase 2 Portion, subjects who discontinue from treatment or the study will not be replaced.

9.5 Treatment

9.5.1 Treatments Administered

The Investigator must ensure that the investigational product will be used only in accordance with the protocol.

Phase 1 Portion

During the Phase 1 Portion of the study, vadastuximab talirine (SGN-CD33A) will be administered every 4 weeks (after azacitidine on the last day of azacitidine administration) via IV push at the assigned dose level (3 to 20 mcg/kg), based on the dose evaluation cohort.

Subjects will also receive azacitidine 75 mg/m^2 SC or IV (at the Investigator's discretion) for 7 days (7 consecutive days or 5 days on/2 days off/2 days on), beginning on Day 1 of repeated 4-week cycles.

Phase 2 Portion

During the Phase 2 Portion of the study, subjects will be randomized to receive either vadastuximab talirine (SGN-CD33A) administered every 4 weeks (after azacitidine on the last day of azacitidine administration) via IV push at the dose determined in the Phase 1 Portion or placebo every 4 weeks (after azacitidine on the last day of azacitidine administration) via IV push.

All subjects will also receive azacitidine 75 mg/m^2 SC or IV (at the Investigator's discretion) for 7 days (7 consecutive days or 5 days on/2 days off/2 days on), beginning on Day 1 of repeated 4-week cycles.

9.5.1.1 Required Premedication and Postmedication

Subjects receiving azacitidine should be premedicated for the prevention of nausea and vomiting according to institutional practice.

Prophylaxis/treatment of hematologic toxicity and infection may be administered according to institutional practice.

9.5.1.2 Vadastuximab Talirine

Detailed information describing the preparation, administration, and storage of vadastuximab talirine is located in the Pharmacy Binder.

9.5.1.2.1 Description

Vadastuximab talirine is a sterile, preservative-free, lyophilized cake or powder, supplied in single-use amber vials. See the Pharmacy Binder for further information.

9.5.1.2.2 Method of Procurement

Vadastuximab talirine and matching placebo will be provided by the Sponsor.

9.5.1.2.3 Dose and Administration

Administration of SGN-CD33A will be via IV push. It is recommended that SGN-CD33A be administered via central venous access port (eg, 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. Due to potential for severe tissue damage, monitor the injection site closely for redness, swelling, pain, infection during and at any time after administration. Advise patients to report redness or discomfort promptly at the time of administration or after infusion. Follow institutional guidelines for the administration of chemotherapy and take precautions to prevent extravasation per institutional standards and as described by Schulmeister. [25]

Depending on the lot of study treatment supplied, a sterile 0.2-mcm filter may be required for administration; see the Pharmacy Binder for details. 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.

Vadastuximab talirine will be administered in repeated 4-week cycles after azacitidine on the last day of azacitidine treatment, via IV push.

During the Phase 1 Portion of the study, the dose level will be determined according to the dose-escalation schedule.

During the Phase 2 Portion of the study, the dose level will be the dose level selected by the SMC based on the phase 1 data. Subjects in the Phase 2 Portion of the study will receive either vadastuximab talirine or matching placebo.

Dosing is based on subject weight. Doses will be adjusted for subjects who have a ≥10% change in weight from baseline. **An exception to weight-based dosing is made for subjects weighing greater than 100 kg; doses will be based on 100 kg for these individuals.** Refer to the Pharmacy Binder for further details.

9.5.1.2.4 Preparation

Vadastuximab talirine vials are provided via single-use containers. Any partially used vials or diluted dosing solutions should be discarded using appropriate institutional drug disposal procedures.

Vadastuximab talirine drug product is reconstituted with sterile Water for Injection (WFI), United States Pharmacopeia (USP) or equivalent, for IV administration. The reconstituted vadastuximab talirine drug product is a clear to slightly opalescent, colorless to light yellow solution. Depending on the dose level, the reconstituted solution is either used directly, or subsequently diluted in sterile 0.9% Sodium Chloride for Injection, USP or equivalent, for IV administration.

Detailed drug preparation instructions are provided in the Pharmacy Binder.

9.5.1.2.5 Study Treatment Labeling and Packaging

Vadastuximab talirine is the International Nonproprietary Name (INN) assigned to SGN-CD33A. Drug product vials may be labeled as SGN-CD33A or as vadastuximab talirine; the 2 names can be used interchangeably.

9.5.1.2.6 Study Treatment Storage and Accountability

It is forbidden to use investigational drug material for purposes other than as defined in this protocol.

<u>Study Treatment Storage</u>

Vials containing vadastuximab talirine must be stored under refrigeration at 2-8°C, protected from light (both sunlight and artificial light).

The chemical and physical stability of the reconstituted drug product has been demonstrated for 24 hours at 2-8°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 2-8°C. If dilution is needed, the reconstituted drug product should be diluted in 0.9% Sodium Chloride Injection, USP, or equivalent, at the time of use. The prepared dosing solution (reconstituted drug product or drug product dilution) should be used within 4 hours after exposing to ambient temperature and light conditions.

Study Treatment Accountability

Drug accountability instructions are provided in the Pharmacy Binder.

9.5.1.3 Azacitidine

Azacitidine is marketed in the US as VIDAZA® by Celgene Corporation Summit, NJ USA. Please refer to the approved US prescribing information (USPI) for detailed information.

9.5.1.3.1 Description

Azacitidine is a pyrimidine nucleoside analog of cytidine.

9.5.1.3.2 Method of Procurement

Commercially available azacitidine will be provided by the study sites from their usual suppliers.

9.5.1.3.3 Dose and Administration

The starting dose for the first treatment cycle for all subjects is 75 mg/m^2 SC or IV (at the Investigator's discretion), 7 days per cycle, either on the first 7 days or 5 days on/2 days off/ 2 days on.

9.5.1.3.4 Preparation

Azacitidine will be prepared for SC or IV administration according to the USPI and local standard of care.

9.5.1.3.5 Storage and Accountability

Azacitidine must be stored, distributed, and disposed of according to institutional practice and the USPI.

9.5.1.4 Management of Adverse Reactions

9.5.1.4.1 Management of Infusion Reactions

Infusions should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal subject care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for infusion-related reactions.

9.5.1.4.2 Overdose

In the event of an overdose ≥10%, the site should notify the sponsor as soon as they are aware of the overdose.

9.5.1.4.3 Dose Modifications

Common toxicities including myelosuppression, nausea, gastrointestinal toxicity, fatigue, pyrexia, headache, weight decrease, dyspnea, rash, and stomatitis should be managed according to institutional standards or accepted guidelines (eg, American Society of Clinical Oncology [ASCO] guidelines for the use of WBC growth factors [26]). Growth factor support may be administered as needed according to institutional standard of care.

Vadastuximab Talirine

Table 2 describes guidelines for dose modifications of vadastuximab talirine (Phase 1 Portion) or blinded study treatment (Phase 2 Portion) for toxicity.

Dose delays of any study treatment are permitted. If dosing is delayed for azacitidine, vadastuximab talirine (Phase 1 Portion), or blinded study treatment (Phase 2 Portion), both study treatments should be held and resumed together on the same schedule except when one agent is omitted during a cycle due to toxicity.

For patients who achieve a response to therapy, dose decreases, delays, or dose re-escalation (to original dose level) are permitted at the discretion of the medical monitor and site Investigator. Following achievement of marrow blast clearance to <5% (ie, a CR or marrow CR), patients originally treated with a dose higher than 5 mcg/kg of study drug will receive azacitidine with vadastuximab talirine (Phase 1 Portion) or blinded study treatment (Phase 2 Portion) as continuation therapy at the maintenance dose of 5 mcg/kg in subsequent cycles.

Azacitidine, vadastuximab talirine (Phase 1 Portion), or blinded study drug (Phase 2 Portion) may be permanently discontinued in the event of unacceptable related toxicity. Subjects will not be considered off study treatment until both study treatments are discontinued.

If subjects become candidates for stem cell transplant after enrollment, vadastuximab talirine must be discontinued at least 30 days prior to initiation of preparative regimen for stem cell transplant.

Table 2: Dose Modifications for Vadastuximab Talirine-Associated Toxicity

Category	Event	Action
Hematologic toxicity with marrow blast count <5%[a]	≥ Grade 3 neutropenia or thrombocytopenia	Cycles of treatment may be delayed up to 14 days[b] until hematologic recovery is observed. Adequate hematologic recovery is defined as neutropenia and thrombocytopenia improved to < grade 3 (unsupported), OR ANC / platelets ≥ [(NADIR COUNT[c]) + (BASELINE COUNT[d] – NADIR COUNT) x 0.50] If hematologic recovery as defined above has not occurred within 14 days of the end of the cycle (by Day 42), omit vadastuximab talirine (Phase 1) or blinded study treatment (Phase 2) from the next cycle, and initiate next dose of azacitidine based on marrow cellularity as defined in Table 3.
Hematologic toxicity with marrow blasts ≥5%[b]	≥ Grade 3 neutropenia or thrombocytopenia	Treatment may continue without dose modification.
Clinically significant non-hematologic toxicity or asymptomatic non-hematologic laboratory abnormality (with the exception of hepatic toxicity)	≥ Grade 3 event	Treatment delay of up to 14 days is permitted until resolution of toxicity to < grade 3.
Laboratory evidence of hepatic toxicity (elevation in ALT, AST, or total bilirubin)	≥ Grade 3 event	Treatment delay of up to 14 days is required until resolution of toxicity to ≤ grade 1 or baseline. If toxicity has not resolved within 14 days, permanently discontinue vadastuximab talirine (Phase 1) or blinded study treatment (Phase 2)

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase.

a If cytopenias above grade 3 (e.g., ANC <1000/mm^3 or platelets <50 x 10^9/L) are present at Day 28 of a cycle in which no response assessment is required, an 'unscheduled' bone marrow biopsy is required within 14 days of the scheduled end of the cycle (eg, between Day 28 and Day 42). If the bone marrow cellularity is ≤10%, vadastuximab talirine or blinded study treatment will be permanently discontinued. If marrow cellularity is >10%, follow guidance as above.

b Delays of >14 days may be permitted with approval of the medical monitor.

c Nadir Count = the lowest count reached during the treatment cycle.

d Baseline Count = counts prior to Cycle 1 of study treatment.

Azacitidine

Dose modifications to azacitidine, including permanent discontinuation due to toxicity, are at the discretion of the treating physician and should adhere to the USPI, the summary of product characteristics (SMPC), or institutional guidelines/standards. Recommended schedule modifications for azacitidine in patients with delayed count recovery and <5% blasts are provided in Table 3.

Table 3: Recommended Scheduled Modifications for Azacitidine in Patients with <5% Blasts and Incomplete Hematologic Recovery at Day 42[a]

Bone Marrow Cellularity:	**>30%**	**15-30%**	**<15%**
Timing of Next Cycle	Next cycle may begin	Delay next cycle until ANC and platelets ≥ [(NADIR COUNT) + (BASELINE COUNT – NADIR COUNT) x 0.50]	Delay next cycle until ANC and platelets ≥ [(NADIR COUNT) + (BASELINE COUNT – NADIR COUNT) x 0.75]

a If vadastuximab talirine (Phase 1) or blinded study drug (Phase 2) was omitted during the previous cycle, consider dose reduction of azacitidine to 50% upon initiation of next cycle.

9.5.2 Blinding of Study Medication

The Phase 1 Portion of this study is an open-label study.

The Phase 2 Portion will be double-blinded. Subjects will receive vadastuximab talirine or matching placebo at the volume equivalent dose level determined in the Phase 1 Portion. The subject and all personnel involved with the conduct and the interpretation of the study, including the investigators, study center personnel, and the Seattle Genetics, Inc., PRA Health Sciences, or designee staff, will be blinded to the medication allocation. Randomization data will be assigned via a centralized interactive voice and web recognition system (IXRS) and kept strictly confidential and accessible only to authorized persons per Seattle Genetics, Inc. (or designee's) Standard Operating Procedures (SOPs) until the time of unblinding.

A randomization number will be assigned to each subject by the IXRS after eligibility is determined. At the initiation of the study, the study center will receive instructions for unblinding a subject using the IXRS. In the event that an emergency unblinding is required, authorized/approved randomization system users will have the ability to retrieve subject treatment group assignment through the randomization system. Unblinding a subject should only be done in emergency situations for reasons of subject safety. The Investigator/study center should make every attempt to contact the Seattle Genetics, Inc. or designee's medical monitor before breaking the blind. When the Investigator contacts the IXRS, the system will guide the Investigator to access the emergency unblinding option. When the blinding code is broken, the reason must be fully documented in the source documentation.

9.5.3 Prior and Concomitant Therapy

Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy, systemic anti-neoplastic therapy, or allogeneic stem cell transplant during the study treatment period.

Any other treatment (not explicitly excluded) considered necessary for the subject's welfare may be given at the discretion of the Investigator. Administration of concomitant medications must be reported in the appropriate section of the eCRF along with dates of administration and reasons for use.

Prophylactic antiemetics should be administered according to institutional standards.

The use of transfusions, platelet and/or colony stimulating factors per institutional practice is permitted. In addition, the ASCO guideline for the use of WBC growth factors is recommended for the management of neutropenia and febrile neutropenia. [26]

All subjects who discontinue the study medication should be offered alternative treatment if applicable. Treatment should be given according to normal clinical practice, after a termination visit (see Section 10.2.2).

9.5.4 Treatment Compliance

Vadastuximab talirine or matching placebo and azacitidine will be administered by qualified study site staff, and administration information will be recorded in the eCRF.

9.5.5 Assignment to Treatment

During the Phase 1 Portion, subjects will be assigned sequentially to the dose level open at the time of enrollment.

During the Phase 2 Portion of the study, after eligibility is determined and within 1 business day of the planned first dose of study treatment, subjects will be randomized to treatment by an IXRS. Subjects will be stratified at randomization by ECOG performance score (0 vs 1 or 2) and IPSS risk category (Intermediate-2 vs High risk).

9.6 Efficacy and Safety Variables

9.6.1 Efficacy and Safety Measurements Assessed

9.6.1.1 Efficacy Measurements

Primary Efficacy Criteria:

The primary efficacy endpoint of this study is ORR.

Subjects will undergo routine laboratory tests (CBCs) and bone marrow examinations. Response status will be assessed according to the IWG Response Criteria in Myelodysplasia. [22] Detailed response definitions are presented in Appendix 18.6.

Secondary Efficacy Criteria:

Secondary efficacy endpoints will be the following:

- Complete response (CR) rate
- Hematologic improvement (HI) rate
- Duration of response (DOR)

- Progression-free survival (PFS)
- Rate of transformation to AML
- Overall survival (OS)

See Section 13.6.4 for definitions.

9.6.1.2 Pharmacokinetic and Antitherapeutic Antibody Assessments

Blood samples for PK and ATA assessment will be collected at the time points outlined in Table 5 and Table 6 (below). Sensitive, qualified assays will be used to measure concentrations of ADC (vadastuximab talirine) and SGD-1882 in plasma and ATAs 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 liquid chromatography/tandem mass spectrometry assays, as well as other assays if further characterization is required. A qualified electrochemiluminescence assay will be used to assess ATA.

9.6.1.3 Biomarker Assessments

Peripheral blood and bone marrow aspirates will be collected at the time points outlined in Table 5 and Table 6 (below). Biomarker assessments may include CD33 expression level, abundance of MDSC, characterization of leukocyte subpopulations in PBMCs, variation in sequence of CD33 and genes commonly mutated in MDS and hematologic malignancies, soluble CD33, abundance of a variety of cytokines, and testing for PNH and HLA-DR15 at protocol-specified time points. Methods of analysis may include flow cytometry, ELISA, DNA, and RNA sequencing.

9.6.1.4 Safety Measurements

Safety assessments will consist of the surveillance of AEs, laboratory test measures, physical examination findings, and concomitant medication records.

10. STUDY EVALUATIONS BY VISIT

A full schedule of study procedures for the screening and treatment periods is provided in Table 4, and schedules of PK, immunogenicity, and biomarker assessments are given in Table 5 and Table 6.

Table 4: Study Schedule

		Baseline/Screening		Enrollment/ Randomization[a]	Each Cycle					EOT[b]	Long-term F/U
					D1	D2-6	D7	D15	D22-29		
	Visit Window	Within 28D prior to study drug	Within 7D prior to study drug	Within 7D prior to study drug	±1D			±1D		30–37 days post last dose	±2 wks
Baseline and Safety Assessments	Informed consent	X		Eligibility documentation submitted to Sponsor prior to study start							
	Inclusion/exclusion	X									
	Medical/MDS history	X									
	Physical examination		X							X	
	Height		X								
	Weight		X		X						
	Vital signs						X[u]				
	Pregnancy test (serum or urine) for women of childbearing potential only		X							X	
	Electrocardiogram		X								
	ECOG performance status		X		X					X	
	Serum chemistry including ferritin		X		X			X[c]		X	
	CBC with differential		X		X			X[c]	X[d]	X	
	Urinalysis[e]		X		X[f]			X[c]		X	
	Inflammatory serologies[g]		X		X[h]					X	
	Specialty autoimmune serologies[i]		X		X[j]					X	
	Concomitant medications and adverse events[t]	Collect any related to study protocol procedures			Collect from predose through 30 days post last dose or EOT visit, whichever is later						
Treatment Administration	Phase 1: vadastuximab talirine[k] Phase 2: blinded study treatment[k]						X[l]				
	Azacitidine[k]				X	X	X[l]				
QoL	PRO questionnaire				X[m]					X	
PK/ATA	Blood samples for PK				See Table 5 (Phase 1 Portion) and Table 6 (Phase 2 Portion)						
	Blood samples for ATA										
Biomarkers	Cytogenetics and gene mutations[n]	X									
	Whole blood for biomarker analysis	See Table 5 (Phase 1 Portion) and Table 6 (Phase 2 Portion)									
	Bone marrow for biomarker analysis[o]										
Response Assessments	Bone marrow examination[p]	X							X[d]	X[r]	X[r]
	Survival status										X[s]

AE = adverse event; ANA = antinuclear antibodies; ANCA = anti-neutrophil cytoplasmic antibodies; anti-dsDNA = anti-double-stranded DNA; ATA = antitherapeutic antibody; CBC = complete blood count; CR = complete response; CRP = C-reactive protein; D = day; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; F/U = follow-up; Ig = immunoglobulin; MDS = myelodysplastic syndrome; PK = pharmacokinetics; PRO = patient reported outcomes; QoL = quality of life; RF = rheumatoid factor.
Please refer to footnotes on following page.

a During the Phase 2 Portion, randomization must be within 1 business day before Cycle 1 Day 1.
b EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.
c Cycles 1 through 4 only.
d Day 22-29 in even-numbered cycles until CR, then every 4 cycles thereafter. If cytopenias above grade 3 (eg ANC <1000/mm^3 or platelets <50 x 10^9/L) are present at Day 28 of a cycle in which no response assessment is required, an 'unscheduled' bone marrow biopsy is required within 14 days of the scheduled end of the cycle (eg, between Day 28 and Day 42) to assess marrow cellularity and blast count, in order to determine if dose / schedule modifications are required in the next cycle..
e Includes urine dipstick or microscopic analysis, as well as spot urine protein and creatinine.
f Even-numbered cycles only.
g Includes clinical laboratory testing for CRP, C3, and C4.
h Cycles 2 and 4 only.
i Includes clinical laboratory testing for ANCA, anti-dsDNA, quantitative immunoglobulins [IgM, IgG, IgA], RF, ANA, and Direct Coomb's].
j Cycle 4 only.
k Alternative schedule of treatment administration permitted: azacitidine 5 days on/2 days off/2 days on and vadastuximab talirine or placebo given on Day 9.
l Day 9 if alternate azacitidine schedule administered.
m Cycles 1, 2, and even-numbered cycles (Cycles 4, 6, 8, etc) thereafter.
n Locally assessed according to institutional standard.
o Portion of bone marrow sample obtained at baseline or for response assessment.
p Bone marrow examination should be based on a bone marrow biopsy; however, if marrow cannot be biopsied, but aspiration is successful, the aspirate may be used to determine blast count. For subjects requiring a marrow evaluation to assess cellularity due to cytopenias, a biopsy is required.
q Only required if not conducted within 4 weeks prior to EOT.
r If study treatment discontinued prior to disease progression or relapse, obtain every 4 months through 24 months after EOT or until initiation of another anticancer treatment, progression, or relapse.
s Contact subject for survival status every 2 months after EOT until death or study closure. Collection of subsequent anticancer treatment information.
t See Sections 10.4 and 12.1.4 for follow-up of adverse events of special interest.
u Before and within 30 minutes after vadastuximab talirine (Phase 1 Portion), or blinded study drug (Phase 2 Portion) administration.

Table 5: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Assessments – Phase 1 Portion

				Whole Blood							Bone Marrow Aspirate		
Cycle	Day	Time	Window	PK	ATA	PNH & HLA-DR15	sCD33, Cytokines & Research	MDSC	CD33 Expression	PBMC	MDSC	CD33 Expression	Mutation Profiling
Baseline/Screening			Within 28 d prior to study drug			X					X[e]	X[e]	X[e]
			Within 7 d prior to study drug							X			
1	1	Pre-azacitidine	within 24 hr		X		X	X	X				
	7 or 9	Pre-vadastuximab talirine	within 24 hr	X			X	X	X		X[i]	X[i]	
		End of vadastuximab talirine administration	within 15 min postdose	X									
		2 hr	± 15 min	X									
		6 hr	± 2 hr	X									
	8[b]	24 hr	± 4 hr	X									
	10[c]	72 hr	± 4 hr	X				X	X				
	15[d]	192 hr	± 4 hr					X	X				
	28		Day 22-29										
2	1	Pre-azacitidine dose	within 24 hr		X		X	X	X	X			
	7 or 9[a]	Pre-vadastuximab talirine	within 8 hr	X									
		End of vadastuximab talirine administration	within 15 min postdose	X									
		2 hr	± 15 min	X									
	8[b]	24 hr	± 4 hr	X									
	10[c]	72 hr	± 4 hr	X									
	28		Day 22-29								X[e]	X[e]	
3	1	Pre-azacitidine	within 24 hr		X								
	7 or 9[a]	End of vadastuximab talirine administration	within 15 min postdose	X									
4+	1	Pre-azacitidine	within 24 hr		X[h]		X[f]	X[f]	X[f]	X[f]			
	7 or 9[a]	End of vadastuximab talirine administration	within 15 min postdose	X[h]									
	28		Day 22-29								X[e,f]	X[e,f]	
End of treatment			30–37 d post last dose		X		X	X	X	X	X[e,g]	X[e,g]	X[e,g]

ATA = antitherapeutic antibody; CR = complete response; d = days; EOT = end of treatment; HLA = human leukocyte antigen; MDSC = myeloid-derived suppressor cells; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetics; PNH = Paroxysmal Nocturnal Hemoglobinuria; sCD33 = soluble CD33.

a Day 9 if vadastuximab talirine is given on Day 9.
b Day 10 if vadastuximab talirine is given on Day 9.
c Day 12 if vadastuximab talirine is given on Day 9.
d Day 17 if vadastuximab talirine is given on Day 9.
e Portion of bone marrow sample obtained at baseline or for response assessment, including at progression.
f Even-numbered cycles until CR, then every 4 cycles thereafter.
g Only required if not conducted within 4 weeks prior to EOT.
h Cycle 4 and every 4 cycles thereafter.
i Cycle 1, Day 7 or 9 bone marrow samples may be up to 48 hours predose.

Table 6: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Assessments – Phase 2 Portion

				Whole Blood							Bone Marrow Aspirate		
Cycle	Day	Time	Window	PK	ATA	PNH & HLA-DR15	sCD33, cytokines & research	MDSC	CD33 expression	PBMC	MDSC	CD33 expression	Mutation Profiling
Baseline/Screening			Within 28 d prior to study drug			X					X[e]	X[e]	X[e]
			Within 7 d prior to study drug										
All	1	Pre-azacitidine dose	within 24 hr		X[b]		X[i]	X[i]	X[i]	X[i]			
	7 or 9[a,c]	Pre dose blinded study drug	within 24/8 hr	X[d]			X[h]	X[h]	X[h]	X[h]			
		End of blinded study drug administration	within 15 min postdose	X[b]									
	28		Day 22-29								X[e,f]	X[e,f]	X[e,f]
End of treatment			30–37 d post last dose		X		X	X	X	X	X[e,g]	X[e,g]	X[e,g]

ATA = antitherapeutic antibody; CR = complete response; d = days; EOT = end of treatment; HLA = human leukocyte antigen; MDSC = myeloid-derived suppressor cells; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetics; PNH = Paroxysmal Nocturnal Hemoglobinuria.

a Cycle 1 Day 7c predose window is 24 hours prior to blinded study treatment administration.
b Required in Cycle 1-4 and every 4 cycles thereafter.
c Day 9 if blinded study treatment given on Day 9.
d Cycles 1-2 only; within 24 hours pre-infusion in Cycle 1 and within 8 hours pre-infusion in Cycle 2.
e Portion of bone marrow sample obtained at baseline or for response assessment, including at progression.
f Even-numbered cycles until CR, then every 4 cycles thereafter.
g Only required if not conducted within 4 weeks prior to EOT.
h Cycle 1 and even-numbered cycles until CR, then every 4 cycles .
i Cycle 1 only.

10.1 Screening (Day -28 to 1)

The following procedures will be performed within 28 days before beginning treatment:

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history, including MDS history (Section 11.1)
- Cytogenetics and gene mutations (Section 11.2)
- Bone marrow examination (Section 11.3)
- Biomarker assessments (Section 11.4)
    - Whole blood (PNH and HLA-DR15)
    - Bone marrow (MDSC, CD33 expression, and mutation profiling)

The following procedures will be performed within 7 days before beginning treatment:

- Physical examination, ECOG performance status, weight, and height (Section 11.5)
- Electrocardiogram (ECG; Section 11.6)
- Serum or urine pregnancy test (women of childbearing potential only)
- Clinical laboratory tests (CBC with differential, serum chemistry including ferritin, and urinalysis; Section 11.7)
- Serology laboratory tests (inflammatory serologies and special autoimmune serologies; Section 11.7)
- Subjects Phase 1 Portion only: Biomarker assessments (Section 11.4)
    - Whole blood (PBMCs).

From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded, as well as any concomitant medications given for the treatment of these AEs.

For Phase 2 Portion only: Within one business day of the planned start of treatment with azacitidine, the study site will contact the IXRS as directed in the study manual. Contact information for the IXRS is provided in the study manual.

10.2 Treatment Period

All subjects will receive treatment in repeated 28-day cycles of azacitidine (75 mg/m^2 SC or IV for 7 consecutive days or 5 days on/2 days off/2 days on) and vadastuximab talirine (after azacitidine on the last day of azacitidine treatment; Section 9.5.1). In addition, procedures will be performed during the treatment period as indicated separately for the Phase 1 Portion (Section 10.2.1) and the Phase 2 Portion (Section 10.2.2), below.

10.2.1 Phase 1 Portion

10.2.1.1 Cycle 1

- Day 1, pretreatment:
    - Biomarker assessments (Section 11.4)
        - Whole blood (sCD33 - cytokines and research; MDSC; and CD33 expression)
    - ECOG performance status and weight (Section 11.5)
    - Clinical laboratory tests (CBC with differential and serum chemistry including ferritin; Section 11.7)
    - PRO questionnaire (Section 11.9)
    - Blood samples for ATAs (within 24 hours before beginning the azacitidine infusion; Section 11.8)
- Days 1 to 6 (if azacitidine is administered on 7 consecutive days) or Days 1 to 5, and 8 (if administered 5 days on/2 days off/2 days on): Administer azacitidine according to the selected treatment schedule (Section 9.5.1.3)
- Day 7 (if azacitidine is administered on 7 consecutive days) or Day 9 (if administered 5 days on/2 days off/2 days on), pretreatment:
    - PK sample collection (within 24 hours before beginning the vadastuximab talirine infusion (Phase 1 Portion; Section 11.4.1)
    - Biomarker assessments (Section 11.4)
        - Whole blood (sCD33 - cytokines and research; MDSC; and CD33 expression)
        - Bone marrow (MDSC and CD33 expression; within 48 hours before beginning the vadastuximab talirine infusion)
    - Vital signs

- After completion of pretreatment procedures, administer azacitidine (Section 9.5.1.3) followed by vadastuximab talirine (Section 9.5.1.2)

- Days 7 to 15 (if azacitidine is administered on 7 consecutive days) or Days 9 to 17 (if administered 5 days on/2 days off/2 days on), posttreatment:
  - Vital signs (Day 7 or 9 only; within 30 minutes after completing the vadastuximab talirine infusion)
  - PK sample collection at the following time points (Section 11.4.1)
    - At the end of the vadastuximab talirine infusion (+15 minutes; Day 7 or Day 9)
    - 2 hours (±15 minutes) after the end of the vadastuximab talirine infusion (Day 7 or Day 9)
    - 6 hours (±2 hours) after the end of the vadastuximab talirine infusion (Day 7 or Day 9)
    - 24 hours (±4 hours) after the end of the vadastuximab talirine infusion (Day 8 or Day 10)
    - 72 hours (±4 hours) after the end of the vadastuximab talirine infusion (Day 10 or Day 12)
  - Whole blood (MDSC and CD33 expression)
    - 72 hours (±4 hours) after the end of the vadastuximab talirine infusion (Day 10 or 12)

- Day 15 (±1 day):
  - Clinical laboratory tests (CBC with differential, serum chemistry including ferritin, and urinalysis; Section 11.7) (±1 day)
  - Whole blood (MDSC and CD33 expression; Section 11.4)
    - 192 hours (±4 hours) after the end of the vadastuximab talirine infusion (Day 10 or 12)

- Day 28 (±7 days):
  - Bone marrow biopsy to assess bone marrow cellularity. Cycle 1 marrow biopsy may be omitted if either a) patient has recovered counts to less than grade 3 cytopenias, ie, absolute neutrophil count (ANC) >1000/mcL AND platelet count >50,000/mcL, without transfusion support, by Day 28 of Cycle 1 or b) there is evidence in the peripheral blood of active MDS, eg, circulating blasts.

Note:

A. *If the marrow is not hypocellular (total marrow cellularity ≥10%), the patient may proceed to Cycle 2 per dose modification guidance, depending on marrow blast percentage / remission status.*

B. *If the marrow is hypocellular (total marrow cellularity <10%), Cycle 2 should be delayed until count recovery (defined in Cycle 1 as thrombocytopenia and neutropenia improving to less than CTCAE grade 4, or by the following formula: [(NADIR COUNT) + (BASELINE COUNT – NADIR COUNT) x 0.75]. If neutrophil count or platelet count have not recovered to less than Grade 4 by Day 42, a repeat marrow should be performed within a week. If the marrow is hypocellular at Day 42, then the subject will have experienced a DLT (posttreatment grade 4 neutropenia or grade 4 thrombocytopenia lasting >42 days from the start of therapy in the absence of evidence of active MDS); if marrow cellularity has recovered to ≥10%, and ongoing cytopenia(s) are attributed to active MDS, then Cycle 2 may be initiated.*

10.2.1.2 Cycle 2

- Day 1 (±1 day), pretreatment:
  - Biomarker assessments (Section 11.4)
    - Whole blood (sCD33 - cytokines and research; MDSC; CD33 expression; and PBMCs)
  - ECOG performance status and weight (Section 11.5)
  - PRO questionnaire (Section 11.9)
  - Clinical laboratory tests (CBC with differential, serum chemistry including ferritin, and urinalysis; Section 11.7)
  - Blood samples for ATAs (within 24 hours before beginning the azacitidine infusion; Section 11.8)
- Days 1 to 6 (if azacitidine is administered on 7 consecutive days) or Days 1 to 5, and 8 (if administered 5 days on/2 days off/2 days on): Administer azacitidine according to the selected treatment schedule (Section 9.5.1.3)
- Day 7 (if azacitidine is administered on 7 consecutive days) or Day 9 (if administered 5 days on/2 days off/2 days on), pretreatment:
  - PK sample collection (within 8 hours before beginning the vadastuximab talirine infusion; Section 11.4.1)
  - Vital signs

- After completion of pretreatment procedures, administer azacitidine (Section 9.5.1.3) followed by vadastuximab talirine (Section 9.5.1.2)

- Days 7 to 15 (if azacitidine is administered on 7 consecutive days) or Days 9 to 17 (if administered 5 days on/2 days off/2 days on), posttreatment:
  - Vital signs (Day 7 or 9 only; within 30 minutes after completing the vadastuximab talirine infusion)
  - PK sample collection at the following time point (Section 11.4.1)
    - At the end of the vadastuximab talirine infusion (+15 minutes; Day 7 or Day 9)
    - 2 hours (±15 minutes) after the end of the vadastuximab talirine infusion (Day 7 or Day 9)
    - 24 hours (±4 hours) after the end of the vadastuximab talirine infusion (Day 8 or 10)
    - 72 hours (±4 hours) after the end of the vadastuximab talirine infusion (Day 10 or 12)

- Day 15 (±1 day):
  - Clinical laboratory tests (CBC with differential, serum chemistry including ferritin, and urinalysis; Section 11.7)

- Day 22 to 29:
  - Clinical laboratory tests (CBC with differential; Section 11.7)
  - Bone marrow examination (Section 11.3)
  - Biomarker assessments (Section 11.4)
    - Bone marrow (MDSC and CD33 expression)

10.2.1.3 Cycle 3

- Day 1 (±1 day), pretreatment:
  - ECOG performance status and weight (Section 11.5)
  - Clinical laboratory tests (CBC with differential and serum chemistry including ferritin; Section 11.7)
  - Blood samples for ATAs (within 24 hours before beginning the azacitidine infusion; Section 11.8)

- Days 1 to 6 (if azacitidine is administered on 7 consecutive days) or Days 1 to 5, 8, and 9 (if administered 5 days on/2 days off/2 days on): Administer azacitidine according to the selected treatment schedule (Section 9.5.1.3)

- Day 7 (if azacitidine is administered on 7 consecutive days) or Day 9 (if administered 5 days on/2 days off/2 days on), pretreatment:

  - Vital signs

- Day 7 (if azacitidine is administered on 7 consecutive days) or Day 9 (if administered 5 days on/2 days off/2 days on), posttreatment:

  - Administer azacitidine (Section 9.5.1.3) followed by vadastuximab talirine (Section 9.5.1.2)

  - Vital signs (within 30 minutes after completing the vadastuximab talirine infusion)

  - PK sample collection (within 15 minutes after completing the vadastuximab talirine infusion; Section 11.4.1)

- Day 15 (±1 day):

  - Clinical laboratory tests (CBC with differential, serum chemistry including ferritin, and urinalysis; Section 11.7)

10.2.1.4 Cycles ≥4

- Day 1 (±1 day), pretreatment:

  - ECOG performance status and weight (Section 11.5)

  - Clinical laboratory tests (Section 11.7)

    - All cycles: CBC with differential and serum chemistry including ferritin

    - Even-numbered cycles only: urinalysis

  - Even-numbered cycles only: PRO questionnaire (Section 11.9)

  - Even-numbered cycles until CR, then every 4 cycles: Biomarker assessments (Section 11.4)

    - Whole blood (sCD33 - cytokines and research; MDSC; CD33 expression; and PBMCs)

  - Cycle 4 only: Serology laboratory tests (inflammatory serologies and special autoimmune serologies; Section 11.7)

    - Cycle 4, then every 4 cycles: Blood samples for ATAs (within 24 hours before beginning the azacitidine infusion; Section 11.8)

- Days 1 to 6 (if azacitidine is administered on 7 consecutive days) or Days 1 to 5, and 8 (if administered 5 days on/2 days off/2 days on): Administer azacitidine according to the selected treatment schedule (Section 9.5.1.3)

- Day 7 (if azacitidine is administered on 7 consecutive days) or Day 9 (if administered 5 days on/2 days off/2 days on), pretreatment:

    - Vital signs

- Day 7 (if azacitidine is administered on 7 consecutive days) or Day 9 (if administered 5 days on/2 days off/2 days on), posttreatment:

    - Administer azacitidine (Section 9.5.1.3) followed by vadastuximab talirine (Section 9.5.1.2)

    - Vital signs (within 30 minutes after completing the vadastuximab talirine infusion)

    - Cycle 4, then every 4 cycles: PK sample collection (within 15 minutes after completing the vadastuximab talirine infusion; Section 11.4.1)

- Day 15 (±1 day):

    - Cycle 4 only: Clinical laboratory tests (CBC with differential, serum chemistry including ferritin, and urinalysis; Section 11.7)

- Day 22 to 29: Even-numbered cycles until CR, then every 4 cycles:

    - Clinical laboratory tests (CBC with differential; Section 11.7)

    - Biomarker assessments (Section 11.4)

        - Bone marrow (MDSC and CD33 expression)

    - Bone marrow examination (Section 11.3)

Any AEs (Section 12.1) and serious adverse events (SAEs; Section 12.1.1), reported or observed, will be reported on the eCRF, and SAEs will be reported as indicated in Section 12.1.5. Any changes in concomitant medications will be recorded at each visit or as they are reported.

10.2.2 Phase 2 Portion

The subject will receive treatment in repeated 28-day cycles of azacitidine (75 mg/m^2 SC or IV for 7 consecutive days or 5 days on/2 days off/2 days on) and/or blinded study medication (vadastuximab talirine or placebo; Section 9.5.1). In addition, procedures will be performed as indicated below.

10.2.2.1 Cycle 1

- Day 1, pretreatment:
  - Biomarker assessments (Section 11.4)
    - Whole blood (sCD33 - cytokines and research; MDSC; CD33 expression; and PBMCs)
  - ECOG performance status and weight (Section 11.5)
  - Clinical laboratory tests (CBC with differential and serum chemistry including ferritin; Section 11.7)
  - PRO questionnaire (Section 11.9)
  - Blood samples for ATAs (within 24 hours before beginning the azacitidine infusion; Section 11.8)
- Days 1 to 6 (if azacitidine is administered on 7 consecutive days) or Days 1 to 5, and 8 (if administered 5 days on/2 days off/2 days on): Administer azacitidine according to the selected treatment schedule (Section 9.5.1.3)
- Day 7 (if azacitidine is administered on 7 consecutive days) or Day 9 (if administered 5 days on/2 days off/2 days on), pretreatment:
  - PK sample collection (within 8 hours before beginning the blinded study medication) (Section 11.4.1)
  - Biomarker assessments (Section 11.4)
    - Whole blood (sCD33 - cytokines and research; MDSC; CD33 expression; and PBMCs)
  - Vital signs
  - After completion of pretreatment procedures, administer azacitidine (Section 9.5.1.3) followed by blinded study medication (Section 9.5.1.2)
  - Vital signs (within 30 minutes after completing the blinded study medication infusion)
  - PK sample collection (within 15 minutes after completing the blinded study medication infusion; Section 11.4.1)
- Day 15 (±1 day):

- Clinical laboratory tests (CBC with differential, serum chemistry including ferritin, and urinalysis; Section 11.7)

10.2.2.2 Cycle 2

- Day 1 (±1 day), pretreatment:
  - ECOG performance status and weight (Section 11.5)
  - PRO questionnaire (Section 11.9)
  - Clinical laboratory tests (CBC with differential, serum chemistry including ferritin, and urinalysis; Section 11.7)
  - Serology laboratory tests (inflammatory serologies; Section 11.7)
  - Blood samples for ATAs (within 24 hours before beginning the azacitidine infusion; Section 11.8)
- Days 1 to 6 (if azacitidine is administered on 7 consecutive days) or Days 1 to 5, and 8 (if administered 5 days on/2 days off/2 days on): Administer azacitidine according to the selected treatment schedule (Section 9.5.1.3)
- Day 7 (if azacitidine is administered on 7 consecutive days) or Day 9 (if administered 5 days on/2 days off/2 days on), pretreatment:
  - PK sample collection (within 8 hours before beginning the blinded study medication infusion; Section 11.4.1)
  - Whole blood (sCD33 - cytokines and research; MDSC; CD33 expression; and PBMCs)
  - Vital signs
  - After completion of pretreatment procedures, administer azacitidine (Section 9.5.1.3) followed by blinded study medication (Section 9.5.1.2)
  - Vital signs (within 30 minutes after completing the blinded study medication infusion)
  - PK sample collection (within 15 minutes after completing the blinded study medication infusion; Section 11.4.1)
- Day 15 (±1 day):
  - Clinical laboratory tests (CBC with differential, serum chemistry including ferritin, and urinalysis; Section 11.7)

- Day 22 to 29:
    - Clinical laboratory tests (CBC with differential; Section 11.7)
    - Bone marrow examination (Section 11.3)
    - Biomarker assessments (Section 11.4)
        - Bone marrow (MDSC, CD33 expression, and mutation profiling)

10.2.2.3 Cycle 3

- Day 1 (±1 day), pretreatment:
    - ECOG performance status and weight (Section 11.5)
    - Clinical laboratory tests (CBC with differential and serum chemistry including ferritin; Section 11.7)
    - Blood samples for ATAs (within 24 hours before beginning the azacitidine infusion; Section 11.8)
- Days 1 to 6 (if azacitidine is administered on 7 consecutive days) or Days 1 to 5, and 8 (if administered 5 days on/2 days off/2 days on): Administer azacitidine according to the selected treatment schedule (Section 9.5.1.3)
- Day 7 (if azacitidine is administered on 7 consecutive days) or Day 9 (if administered 5 days on/2 days off/2 days on), pretreatment:
    - Vital signs
- Day 7 (if azacitidine is administered on 7 consecutive days) or Day 9 (if administered 5 days on/2 days off/2 days on), posttreatment:
    - Administer azacitidine (Section 9.5.1.3) followed by blinded study medication (Section 9.5.1.2)
    - Vital signs (within 30 minutes after completing the blinded study medication infusion)
    - PK sample collection (within 15 minutes after completing the blinded study medication infusion; Section 11.4.1)
- Day 15 (±1 day):
    - Clinical laboratory tests (CBC with differential, serum chemistry including ferritin, and urinalysis; Section 11.7)

10.2.2.4 Cycles ≥4

- Day 1 (±1 day), pretreatment:
  - ECOG performance status and weight (Section 11.5)
  - Even-numbered cycles only: PRO questionnaire (Section 11.9)
  - Clinical laboratory tests (Section 11.7)
    - All cycles: CBC with differential and serum chemistry including ferritin
    - Even-numbered cycles only: urinalysis
  - Even-numbered cycles until CR, then every 4 cycles: Biomarker assessments (Section 11.4)
    - Whole blood (sCD33 - cytokines and research; MDSC; CD33 expression; and PBMCs)
  - Cycle 4 only: Serology laboratory tests (inflammatory serologies and special autoimmune serologies; Section 11.7)
  - Cycle 4, then every 4 cycles: Blood samples for ATAs (within 24 hours before beginning the azacitidine infusion; Section 11.8)
- Days 1 to 6 (if azacitidine is administered on 7 consecutive days) or Days 1 to 5, and 8 (if administered 5 days on/2 days off/2 days on): Administer azacitidine according to the selected treatment schedule (Section 9.5.1.3)
- Day 7 (if azacitidine is administered on 7 consecutive days) or Day 9 (if administered 5 days on/2 days off/2 days on), pretreatment:
  - Vital signs
- Day 7 (if azacitidine is administered on 7 consecutive days) or Day 9 (if administered 5 days on/2 days off/2 days on), posttreatment:
  - Administer azacitidine (Section 9.5.1.3) followed by blinded study medication (Section 9.5.1.2)
  - Vital signs (within 30 minutes after completing the blinded study medication infusion)
  - Cycle 4, then every 4 cycles: PK sample collection (within 15 minutes after completing the blinded study medication infusion; Section 11.4.1)

- Day 15 (±1 day):
    - Cycle 4 only: Clinical laboratory tests (CBC with differential, serum chemistry including ferritin, and urinalysis; Section 11.7)
- Day 22 to 29: Even-numbered cycles until CR, then every 4 cycles:
    - Clinical laboratory tests (CBC with differential; Section 11.7)
    - Biomarker assessments (Section 11.4)
        - Bone marrow (MDSC and CD33 expression)
    - Bone marrow examination (Section 11.3)

Any AEs (Section 12.1) and SAEs (Section 12.1.1), reported or observed, will be reported on the eCRF, and SAEs will be reported as indicated in Section 12.1.5. Any changes in concomitant medications will be recorded at each visit or as they are reported.

10.3 End of Treatment

For all subjects in both portions of the study, an EOT visit will be performed 30 to 37 days after the last dose of study treatment (vadastuximab talirine or placebo and/or azacitidine). At the EOT visit, the following assessments/procedures will be performed:

- Physical examination and ECOG performance status (Section 11.5)
- Serum or urine pregnancy test (women of childbearing potential only)
- Clinical laboratory tests (CBC with differential, serum chemistry including ferritin, urinalysis; Section 11.7)
- Serology laboratory tests (inflammatory serologies and special autoimmune serologies; Section 11.7)
- PRO questionnaire (Section 11.9)
- Bone marrow examination (Section 11.3)
- Blood samples for ATAs (Section 11.8)
- Biomarker assessments (Section 11.4)
    - Whole blood (sCD33 - cytokines and research; MDSC; CD33 expression; and PBMCs)
    - Bone marrow (MDSC; CD33 expression; and mutation profiling) – not required if a sample was collected within the previous 4 weeks

Any AEs (Section 12.1) and SAEs (Section 12.1.1), reported or observed, will be reported on the eCRF, and SAEs will be reported as indicated in Section 12.1.5. End-of-treatment evaluations should be obtained before the initiation of non-protocol therapy. If the EOT visit occurs less than 30 days after the last treatment with any study treatment, the subject will be contacted by telephone 30 to 37 days after the last study treatment to assess any AEs or changes in concomitant medications that may have occurred since the EOT visit.

10.4 Follow-Up

If study treatment is discontinued prior to disease progression or relapse, bone marrow samples will be obtained from assessments conducted every 4 months through 24 months after EOT or until initiation of another anticancer treatment, progression, or relapse.

Events of sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) that occur within 180 days of the last dose of vadastuximab talirine or blinded study drug 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 or blinded study drug in the absence of relapse and additional therapy will be followed for SOS/VOD for 100 days post-transplant.

Subjects will be contacted for survival information and collection of subsequent anticancer treatment information approximately every 2 months until death or study completion.

If subjects become candidates for stem cell transplant after enrollment, initiation of preparative regimen for stem cell transplant should not be performed until at least 30 days after the last dose of vadastuximab talirine. It is recommended to avoid transplant conditioning regimens with higher risk of SOS/VOD, including total-body irradiation and multiple alkylating agents. [27, 28] An association of SOS/VOD in patients with pre-exposure to vadastuximab talirine has not been established.

10.5 End of Study/End of Follow-up

The date the subject met criteria for study discontinuation and the reason for study discontinuation will be collected.

11. METHODS OF ASSESSMENT

11.1 Medical History

A full medical history, including demographic information and history of MDS and comorbidities, will be performed at screening on the eCRF. Any AEs (Section 12.1) occurring after screening and before the first dose of study drug will be included as medical history.

11.2 Cytogenetics and Gene Mutations

Cytogenetics and mutation status at baseline will be assessed locally according to institutional standard and recorded on the eCRF. Additional samples will be assessed for mutation profiling (Section 11.4).

11.3 Bone Marrow Examination

Bone marrow examinations for disease assessment at baseline, on treatment, and during follow-up will be performed according to local standards and recorded on the eCRF. After EOT, bone marrow examinations for disease assessment should be performed every 4 months through 24 months after EOT or until initiation of another anticancer treatment, progression, or relapse. Bone marrow examination should be based on a bone marrow biopsy; however, if marrow cannot be biopsied, but aspiration is successful, the aspirate may be used to determine blast count.

In addition to response assessment time points, a bone marrow biopsy will be performed between Day 28 and Day 42 of any cycle in which the patient has not achieved hematologic recovery (as defined in Table 2). This biopsy is to determine the blast count and marrow cellularity, in order to determine if dose modification / dose delay is required in the subsequent cycle (Table 2 and Table 3). This biopsy to assess cellularity is not required if counts have recovered (ie, ANC >1000/mm^3 AND platelet count >50,000/mm^3, without transfusion support, by Day 28 of the cycle) or if there are circulating blasts in the peripheral blood (as evidence of active MDS).

11.4 Pharmacokinetic and Biomarker Assessments

11.4.1 Pharmacokinetics

Plasma samples will be collected for assessment of ADC (vadastuximab talirine) and SGD-1882. Pharmacokinetic sample collection procedures are detailed in the laboratory manual.

Full-profile PK sample collection will be performed for subjects enrolled in the Phase 1 Portion of the study. In the Phase 1 Portion, samples will be collected at the following time points:

- Cycle 1
    - Day 1: (within 24 hours before azacitidine administration)
    - Day 7 or Day 9 (last day of azacitidine dosing):

        - Within 24 hours before vadastuximab talirine administration
        - At the end of vadastuximab talirine administration (within 15 minutes postdose)
        - 2 hours (±15 minutes) after the end of vadastuximab talirine administration
        - 6 hours (±2 hours) after the end of vadastuximab talirine administration
        - 24 hours (±4 hours) after the end of vadastuximab talirine administration (Day 8 or 10)
        - 72 hours (±4 hours) after the end of vadastuximab talirine administration (Day 10 or 12)
- Cycle 2
    - Day 7 or Day 9 (last day of azacitidine dosing):
        - Within 8 hours before vadastuximab talirine administration
        - At the end of vadastuximab talirine administration (within 15 minutes postdose)
        - 2 hours (±15 minutes) after the end of vadastuximab talirine administration
        - 24 hours (±4 hours) after the end of vadastuximab talirine administration (Day 8 or 10)
        - 72 hours (±4 hours) after the end of vadastuximab talirine administration (Day 10 or 12)
- Cycle 3
    - Day 7 or Day 9 (last day of azacitidine dosing):
        - At the end of vadastuximab talirine administration (within 15 minutes postdose)
- Cycle 4, then every 4 cycles
    - Day 7 or Day 9 (last day of azacitidine dosing):
        - At the end of vadastuximab talirine administration (within 15 minutes postdose)

In the Phase 2 Portion, PK samples will be collected at the following time points:

- Cycle 1
    - Day 7 or Day 9 (last day of azacitidine dosing):

- Within 24 hours before vadastuximab talirine/placebo administration
- At the end of vadastuximab talirine/placebo administration (within 15 minutes postdose)

- Cycle 2
  - Day 7 or Day 9 (last day of azacitidine dosing):
    - Within 8 hours before vadastuximab talirine/placebo administration
    - At the end of vadastuximab talirine/placebo administration (within 15 minutes postdose)

- Cycles 3 and 4, then every 4 cycles
  - Day 7 or Day 9 (last day of azacitidine dosing):
    - At the end of vadastuximab talirine/placebo administration (within 15 minutes postdose)

11.4.2 Biomarker Analyses: Whole Blood

Whole blood samples will be collected for assessment of biomarkers. Antitherapeutic antibody sample collection procedures are detailed in the laboratory manual.

During the Phase 1 Portion of the study, samples will be collected at the following time points:

- Baseline/Screening
  - Within 28 days before Day 1 (PNH and HLA-DR15)
  - Within 7 days before Day 1 (PBMCs): Both baseline/screening samples may be collected at the same time if it is within 7 days before Day 1.

- Cycle 1
  - Day 1: Within 24 hours before azacitidine administration (sCD33 cytokines and research; MDSC; CD33 expression)
  - Day 7 or Day 9 (last day of azacitidine dosing): Within 24 hours before vadastuximab talirine administration (sCD33 cytokines and research; MDSC; CD33 expression)
  - Day 10 or 12: 72 hours (±4 hours) after the end of vadastuximab talirine administration (MDSC; CD33 expression)
  - Day 15 or 17: 192 hours (±4 hours) after the end of vadastuximab talirine administration (MDSC; CD33 expression)

- Cycle 2
    - Day 1: Within 24 hours before azacitidine administration (sCD33 cytokines and research; MDSC; CD33 expression; PBMCs)
- Cycle 4 and even-numbered cycles until CR, then every 4 cycles
    - Day 1: Within 24 hours before azacitidine administration (sCD33 cytokines and research; MDSC; CD33 expression; PBMCs)
- At the EOT visit (30 to 37 days after the last dose of study drug; sCD33 cytokines and research; MDSC; CD33 expression; PBMCs)

During the Phase 2 Portion of the study, samples will be collected at the following time points:

- Baseline/Screening: Within 28 days before Day 1 (PNH and HLA-DR15)
- Cycle 1
    - Day 1: Within 24 hours before azacitidine administration (sCD33 cytokines and research; MDSC; CD33 expression; and PBMCs)
    - Day 7 or Day 9 (last day of azacitidine dosing): Within 8 hours before vadastuximab talirine/placebo administration (sCD33 cytokines and research; MDSC; CD33 expression; and PBMCs)
- Cycle 2 and even-numbered cycles thereafter (Cycles 4, 6, 8, etc) until CR, then every 4 cycles
    - Day 7 or Day 9 (last day of azacitidine dosing): Within 8 hours before vadastuximab talirine/placebo administration (sCD33 cytokines and research; MDSC; CD33 expression; and PBMCs)
- At the EOT visit (30 to 37 days after the last dose of study drug; sCD33 cytokines and research; MDSC; CD33 expression; PBMCs)

11.4.3 Biomarker Analyses: Bone Marrow Aspirate

A portion of the bone marrow samples (aspirate) collected for disease assessment at baseline, for response assessment, and at the time of progression will be preserved for biomarker analyses. If baseline sample is collected prior to consent, a separate bone marrow aspirate will be collected for biomarker analyses. Sample collection and preparation procedures are detailed in the laboratory manual.

During the Phase 1 Portion of the study, samples will be collected at the following time points:

- Baseline/Screening (within 28 days before Day 1; MDSC; CD33 expression; mutation profiling)

- Cycle 1
    - Day 7 or Day 9: Within 24 hours before vadastuximab talirine administration (MDSC; CD33 expression)
- Cycle 2 and even-numbered cycles thereafter until CR, then every 4 cycles
    - Day 22-29 (MDSC; CD33 expression)
- At the EOT visit (30 to 37 days after the last dose of study drug; MDSC; CD33 expression; mutation profiling). An EOT sample is not required if a sample was collected within the previous 4 weeks.

During the Phase 2 Portion of the study, samples will be collected at the following time points:

- Baseline/Screening: Within 28 days before Day 1 (MDSC; CD33 expression; mutation profiling)
- Cycle 2 and even-numbered cycles thereafter until CR, then every 4 cycles
    - Day 22-29 (MDSC; CD33 expression; mutation profiling)
- At the EOT visit (30 to 37 days after the last dose of study drug; MDSC; CD33 expression; mutation profiling). An EOT sample is not required if a sample was collected within the previous 4 weeks.

11.5 Physical Examination, ECOG Performance Status, Weight, and Vital Signs

Physical examinations will be performed within 7 days before starting treatment and will include examination of the following: head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system, and nervous system. Postscreening physical examinations may be focused, at the discretion of the Investigator, to identify changes from baseline.

ECOG performance status (Appendix 18.3) will be assessed at the time points indicated in Table 4 and recorded on the eCRF.

Body weight (kg) and height (cm) will be determined within 7 days before starting treatment to assess body surface area (to be recorded in the eCRF).

Vital signs (including temperature, heart rate, respiratory rate, and blood pressure) will be assessed at the time points indicated in Table 4 and recorded on the eCRF.

11.6 Electrocardiograms

ECG recordings will be obtained within 7 days before starting treatment. A copy of all ECGs will be retained on site.

For the purposes of screening, the Investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically acceptable for inclusion, if abnormal.

ECGs may be repeated for quality reasons, and additional ECGs may be collected by the Investigator for safety reasons. Any posttreatment clinically relevant abnormal ECG findings will be reported as AEs.

11.7 Clinical Laboratory Tests

For all women of childbearing potential, serum or urine pregnancy tests will be performed locally at screening and at EOT.

Screening laboratory assessments to determine eligibility will be performed locally by certified laboratories.

Postscreening, all protocol-required laboratory assessments will be performed by the central laboratory to evaluate safety at the times indicated in Table 4. Additional local laboratory testing may be performed for evaluating safety and making clinical decisions.

The following parameters will be determined by the central laboratory:

Hematology: WBC count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell count, platelet count, and hemoglobin/hematocrit.

Clinical chemistry: Albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, ferritin, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, uric acid, lipase, and amylase.

Creatinine clearance will be calculated using the Cockcroft-Gault [24] formula:

Male subjects	Creatinine clearance (mL/min)	=	$\frac{[140 - \text{Age (years)}] \times \text{body weight (kg)}}{72 \times \text{serum creatinine}}$
Female subjects	Creatinine clearance (mL/min) =	$0.85 \times$	$\frac{[140 - \text{Age (years)}] \times \text{body weight (kg)}}{72 \times \text{serum creatinine}}$

Urinalysis: Urine dipstick or microscopic analysis, as well as spot urine protein and creatinine will be performed locally as indicated in Table 4.

Inflammatory serologies: C-reactive protein (CRP), C3, and C4.

Specialty autoimmune serologies: Anti-neutrophil cytoplasmic antibodies (ANCA), anti-double-stranded DNA (anti-dsDNA), quantitative immunoglobulins (IgM, IgG, IgA), rheumatoid factor (RF), antinuclear antibodies (ANA), and Direct Coomb's.

Additional laboratory assessments, as necessary for subject management, may be performed by certified local laboratories. Documentation of certification will be filed with study documentation.

Central laboratory results will not be provided to the study sites. Additional and repeat laboratory safety testing may be performed at the discretion of the Investigator.

11.8 Blood Samples for Antitherapeutic Antibodies

11.8.1 Antitherapeutic Antibodies

Serum samples will be collected for assessment of ATAs. Antitherapeutic antibody sample collection procedures are detailed in the laboratory manual.

Sample collection for ATAs will be performed for all subjects enrolled in both phases of the study before treatment with vadastuximab talirine/placebo (on Day 7 or Day 9) in Cycles 1-4 and in every 4 cycles thereafter. The sample collection window is within 24 hours pretreatment in Cycle 1 and within 8 hours pretreatment for other cycles.

11.9 Quality of Life Data Collection

Quality of life will be assessed by using the PRO tool QLQ-C30. The QLQ-C30 is a validated QoL/PRO tool [29 and Appendix 18.7] and will be assessed pretreatment on Day 1 of Cycles 1 and 2 and even-numbered cycles thereafter (ie, Cycles 4, 6, 8, etc) and at EOT. The subject will be instructed to fill out the questionnaires to the best of his/her abilities, and the study staff will be responsible for confirming that the subject has completed the questionnaires.

11.10 Response Assessment

Response will be assessed according to the 2006 IWG criteria [22] as outlined in Section 13.6.4.1 and Appendix 18.6. Disease assessments (blood and bone marrow) will be performed at the end of each even-numbered cycle (Day 22-29) until CR, then every 4 cycles thereafter (Table 4) according to local practice.

12. SAFETY MEASUREMENTS AND VARIABLES

12.1 Adverse Events

12.1.1 Definitions

Adverse Events

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a subject 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 eCRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and postdose) through the end of the safety reporting period (see Section 12.1.3). Complications that occur in association with any procedure (eg, 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 an 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 (eg, 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 AE 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 serious AEs 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 (Appendix 18.4). 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 SAEs).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study drug (vadastuximab talirine or azacitidine) 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 (eg, 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 (eg, tendon rupture)
Unrelated:	Another cause of the AE is more plausible (eg, 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

12.1.2 Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs, whether elicited during subject questioning, discovered during physical examination, laboratory testing, and/or other means by recording them on the eCRF 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 eCRF:

- 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 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 AE.

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 primary event on both the eCRF and an SAE form; events occurring secondary to the primary event should be described on the SAE form in the narrative description of the case.

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 eCRF.

- 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' when reporting an AE because it is too general. Instead, report the specific disease (clinical) manifestation of the progression (eg, 'malignant pleural effusion', 'spinal bone metastases', 'lymphadenopathy from underlying non-Hodgkin lymphoma', 'brain metastases').

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 subject. Only report pregnancies that occur in a male subject's partner if the estimated date of conception is after the male subject's first study drug dose. Fax or email 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 eCRF: 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 eCRF.

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 12.1.1) should be reported as SAEs.

12.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through 30 days after the last dose of study treatment (vadastuximab talirine or azacitidine). However, all study protocol-related AEs are to be collected from the time of informed consent.

All SAEs that occur after the end of safety reporting period (ie, more than 30 days after the last dose of study treatment) and are considered treatment-related in the opinion of the Investigator should also be reported to the Sponsor.

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, or the subject dies or withdraws consent, or study closure. All non-serious AEs will be followed through the safety reporting period.

12.1.4 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 according to safety reporting requirements. Events of SOS/VOD that occur within 180 days of the last dose of vadastuximab talirine or blinded study drug 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 or blinded study drug in the absence of relapse and additional therapy will be followed for SOS/VOD for 100 days post-transplant.

12.1.5 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:

- Subject 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 faxed to the Sponsor's Drug Safety Department at **(425) 527-4308** or drug.safety@seagen.com within 24 hours.

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

12.1.6 Sponsor Safety Reporting Requirements in the United States

According to 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), 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 FDA as individual IND safety reports.

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 Seattle Genetics' Drug Safety Department. If, upon review, an SAE is occurring at a higher rate than that which would be expected for the study population, then an IND safety report for the SAE will be submitted to the FDA.

These safety reporting requirements apply only to the process by which the Sponsor reports SAEs to the FDA. Investigators are required to report all SAEs, including anticipated SAEs, to the Sponsor. In addition, the Sponsor will report all SAEs to international authorities as required per local regulatory reporting requirements.

13. DATA MANAGEMENT AND STATISTICAL ANALYSIS

The data management and statistical analysis of this study will be performed by an external clinical research organization (CRO) PRA Health Sciences.

13.1 Data Management

An eCRF will be used for the current study, and a data management plan will be prepared by the CRO PRA Health Sciences.

Previous and concomitant medications will be coded using the latest available WHO Drug Reference Dictionary. Coexistent diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between Seattle Genetics, Inc., and the PRA Health Sciences project team.

13.2 Sample Size Estimation

Phase 1 Portion (minimum of 6 subjects per cohort): Six subjects are adequate to appropriately assess the safety profiles and DLT rates of differing dose levels of vadastuximab talirine in combination with azacitidine. If the true incidence rate of DLT is 10%, the probability of considering a dose level tolerable (ie, ≤1 of 6 subjects experiences a DLT) will be 88.6%. If the true incidence rate of DLT is 50%, the probability of considering a dose level tolerable will be 10.9%.

Phase 2 Portion (106 subjects): A sample size of 106 subjects will provide 85% power to detect a treatment difference in ORR, assuming an ORR of 30% for azacitidine alone vs 55% for the combination of vadastuximab talirine with azacitidine, at a 2-sided 0.1 alpha level.

13.3 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written and finalized prior to any lock of the study database. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. Additional analyses may be added. Table, listing, and figure shells will also be provided.

13.4 Randomization

During the Phase 2 Portion of the study, subjects will be randomized in a 1:1 manner to receive azacitidine with or without vadastuximab talirine, stratified by ECOG performance score (0 vs 1 or 2) and IPSS score (Intermediate-2 vs High risk). Randomization will be performed by an IXRS.

13.5 Analysis Populations

13.5.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who are randomized in the Phase 2 Portion of the study. Subjects will be grouped according to their randomized treatment group assignment regardless of the treatment they actually received.

13.5.2 Safety Population

The safety population will include all subjects who are enrolled and received at least 1 dose of study treatment (vadastuximab talirine or azacitidine) in both portions of the study.

13.5.3 DLT-Evaluable Population

The DLT-evaluable population will include all Phase 1 subjects who have completed at least Cycle 1 of treatment (Cycle 1 of treatment is completed when the patient receives the first dose of azacitidine on Day 1 of Cycle 2) *or* discontinued study treatment because of AEs or for a safety-related reason before having had the opportunity to receive the first dose of azacitidine on Day 1 of Cycle 2. Subjects in the DLT-evaluable population will be grouped by assigned dose level.

13.5.4 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will include all ITT subjects who received at least 1 dose of study medication (azacitidine or vadastuximab talirine).

13.5.5 Per-Protocol Population

A per-protocol population may be defined in the SAP.

13.6 Statistical Methods

13.6.1 Missing Data

Missing data will not be imputed, with the exception of missing or partial dates; imputation rules for missing or partial dates will be specified in the SAP.

Time-to-event data will be censored as outlined in Section 13.6.4.2. All other missing data will be treated as missing.

13.6.2 Demographic and Baseline Data

Demographic and baseline data will be summarized descriptively by phase and treatment arm or dose level. For continuous variables, descriptive statistics will include the mean, standard deviation (or standard error), median, range, and interquartile range. For categorical variables, descriptive statistics will include the number and percent. All demographic and baseline data will be listed.

13.6.3 Subject Disposition

The number and percent of subjects who discontinue treatment and withdraw from study and the reasons for discontinuation or withdrawal will be summarized. Disposition by the number of cycles of treatment will be summarized by phase and treatment arm or dose level.

13.6.4 Efficacy

The primary endpoint of the Phase 2 Portion is ORR, and the study will be unblinded for analysis of ORR after all subjects have completed 6 cycles of therapy or have discontinued treatment for any reason before completing 6 cycles. Data collection for the secondary efficacy endpoints and the safety and other endpoints will continue in an unblinded or partially blinded fashion until all subjects have discontinued study treatment.

13.6.4.1 Response to Treatment

Subjects will be assigned a response status based on assessments at each visit as indicated in Table 4. The primary efficacy endpoint of the study is ORR, defined as the proportion of subjects who achieve any category of CR (CR and Marrow CR) or PR based on the 2006 IWG criteria for MDS [22] that are summarized in Appendix 18.6. ORR will be analyzed based on the phase 2 ITT population. ORR will be assessed during the on treatment period until EOT.

The ORR will be summarized by treatment group and the corresponding 90% confidence intervals will be calculated. The treatment difference in ORR will be tested using a Cochran-Mantel-Haenszel test for the Phase 2 Portion of the study.

ORR will be summarized descriptively by dose for the subjects in the Phase 1 Portion of the study who qualified for the safety population.

13.6.4.2 Secondary Efficacy Endpoints

Time-to-event variables (DOR, PFS, and OS) will be summarized descriptively using the Kaplan-Meier estimate. Additional details will be provided in the SAP. Secondary endpoints will be assessed in the ITT population (except as indicated below).

CR Rate: Response (CR/Marrow CR, PR, ORR [CR/Marrow CR+PR], HI rate, stable disease [SD], and PD) will be summarized descriptively by treatment arm. CR rate will be summarized with 90% confidence intervals. Rate of transformation to AML will also be summarized.

DOR (for PR/CR and CR): DOR is defined as the time from first observation of response (PR+CR/Marrow CR or CR/Marrow CR) to disease progression/relapse or death from any cause, whichever occurs first. Durations will be assessed in the ITT population with a PR or CR and calculated separately for subjects with CR/Marrow CR and those with PR+CR/Marrow CR combined. For subjects with a remission without subsequent disease progression/relapse or death on study, DOR will be censored at the time of the last disease assessment demonstrating a lack of disease progression/relapse. Subjects who receive another anti-neoplastic therapy in the absence of documented progression will be censored at the time of receiving off-protocol therapy for

malignancy, EXCEPT that subjects who receive stem cell transplant in remission will continue to be followed for progression.

Progression-free Survival: PFS is defined as the time from first dose of study medication to first documentation of disease progression/relapse, or to death due to any cause, whichever occurs first. For subjects without disease progression/relapse or death on study, PFS will be censored at the time of the last on-study disease assessment demonstrating a lack of disease progression/ relapse. If more than one date of progression is available, the earliest date will be used to determine PFS. Subjects who receive another anti-neoplastic therapy in the absence of documented progression will be censored at the time of receiving off-protocol therapy for malignancy, EXCEPT that subjects who receive stem cell transplant in remission will continue to be followed for progression.

Overall Survival: OS is defined as the time from first dose of study medication to death due to any cause. For subjects not known to have died at the end of the study, OS will be censored at the time the subject was last known to be alive (including follow-up data).

Efficacy endpoints will be summarized descriptively by dose for the subjects in the Phase 1 Portion of the study who qualified for the safety population.

13.6.5 Quality of Life

Data from the QLQ-C30 will be scored as recommended by the European Organization for Research and Treatment of Cancer (see Appendix 18.7) and summarized descriptively.

13.6.6 Pharmacokinetics, Immunogenicity, and Biomarkers

Estimates of selected PK parameters (vadastuximab talirine ADC and SGD-1882), incidence of ATA to vadastuximab talirine, and biomarker data (in whole blood and bone marrow, as outlined in Section 11.4.2 and Section 11.4.3) will be summarized by phase and treatment arm or dose level.

13.6.7 Safety

Safety data will be summarized for the safety population separately for the Phase 1 and Phase 2 Portions by treatment arm or dose level.

Exposure to treatment will be summarized separately for vadastuximab and azacitidine. Summaries will include the duration of treatment, number of doses received, number of cycles received, number of doses interrupted and the reasons for dose interruption, the number of subjects with dose decreases for toxicity, the cumulative dose, and the relative dose intensity.

All AEs reported after initiation of treatment and pre-existing conditions that worsen after initiation of treatment will be considered treatment-emergent AEs (TEAEs). All AEs will be coded by system organ class, MedDRA preferred term, and severity grade using NCI CTCAE (v 4.03; Appendix 18.4). All recorded AEs will be included in the data listings.

The number and percent of subjects reporting all TEAEs, treatment-related AEs, SAEs, and deaths; TEAEs according to worst CTCAE grade; and AEs leading to treatment discontinuation will be summarized by preferred term and, where appropriate, system organ class. Deaths, SAEs, and AEs leading to treatment discontinuation will also be listed.

Adverse events that were considered DLTs will be listed and summarized by dose level for the DLT-evaluable population.

Summary statistics for actual values and for change from baseline will be tabulated as appropriate for laboratory results by scheduled visit. Where appropriate, laboratory results will be graded according to CTCAE 4.03, and shift tables from baseline to worst observed posttreatment grade will be presented.

All medications received during the treatment period will be considered as concomitant medications and will be coded by WHO medical dictionary and summarized.

13.6.8 Additional Data

Additional summaries may be defined in the SAP.

13.6.9 Interim Analysis

No formal interim analyses for efficacy are planned for this study. During the Phase 1 Portion, the SMC will monitor safety in an ongoing fashion. The SMC will comprise medical experts from Seattle Genetics or their designee and a group of the investigators involved in the Phase 1 Portion. Exploratory or other analyses of the open-label phase 1 data may be performed.

During the Phase 2 Portion, an IDMC will periodically assess the ongoing safety data and make recommendations to either continue evaluating the combination or to halt due to toxicity concerns.

13.6.10 Independent Data Monitoring Committee

The IDMC will consist of individuals external to Seattle Genetics, Inc. and PRA Health Sciences, chosen for their expertise in oncology. Members of the IDMC will include, at a minimum, physicians and appropriate statistical representation. The primary role of this IDMC will be to monitor safety data.

The IDMC will review unblinded safety data after the first 20 subjects in the Phase 2 Portion have completed 2 cycles of therapy and then every 6 months thereafter and as needed. The IDMC may recommend changes to the protocol. In addition, the IDMC will communicate major safety concerns and recommendations regarding study modification or termination to Seattle Genetics, Inc. senior management at any time during the conduct of the study.

The safety analysis will evaluate the overall safety of the treatment regimens including, but not limited to, the following parameters:

- Type, incidence, severity, seriousness, and relatedness of AEs

- Incidence of grade ≥3 febrile neutropenia
- Type, incidence, and severity of laboratory abnormalities
- Incidence and severity of infusion-related and hypersensitivity reactions.

Additional details of the safety reviews will be provided in the IDMC charter.

14. MONITORING PROCEDURES (QUALITY ASSURANCE)

The Sponsor has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. As such, in order to fulfill these obligations and to monitor study progress, the Sponsor's monitors or representatives will visit the investigative sites during study conduct, in addition to maintaining telephone and written communication. On-site visits, telephone calls, and regular inspection of the eCRFs will be conducted in order to assess subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The Investigator must provide the monitor with full access to all source and study documents.

14.1 Routine Monitoring

Sponsor assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study subjects considered for study entry for the purpose of verifying entries made in the eCRF, and assisting with their activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

The site must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Whenever a subject name is revealed on a document that is to be collected for the Sponsor, the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification.

14.2 Inspections and Auditing Procedures

The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator or designee should contact the Sponsor/CRO immediately if this occurs. The Investigator must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are fulfilled.

15. STUDY MANAGEMENT AND MATERIALS

15.1 Electronic Case Report Forms

An eCRF will be used to store and transmit subject information. The file structure and format for the eCRF will be provided by the Sponsor or their representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed, electronically signed, and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by examining personnel or the study coordinator. The eCRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

15.2 Data Collection

During each study visit, a physician participating in the study will maintain medical records to document all significant observations. At a minimum, these notes will contain:

- The date of the visit and the corresponding day or visit in the study schedule (eg, screening, Cycle 1, Day 1, etc.)
- General condition and status remarks by the subject, including any *significant* medical findings. The severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether or not the reported AE is study drug-related
- Changes in concomitant medications or dosages
- A general reference to the procedures completed
- The signature or initials of all physicians making an entry in the medical record (progress notes)

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

Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Changes to information in the medical record (progress notes), eCRF, and other source documents will be initialed and dated on the day the change is made by the Investigator or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

15.3 Source Documents Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs, and recorded data from automated instruments.

All source documents from this study will be maintained by the Investigator and made available for inspection by authorized persons. The original signed informed consent for each subject shall be filed with records kept by the Investigator, and a copy shall be given to the subject.

15.4 Record Maintenance

All data derived from the study will remain the property of Seattle Genetics, Inc.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of subjects, source documents, eCRFs, and study drug inventory must be kept on file.

US FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medical inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept for 2 years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified. The Sponsor or their representative will notify the Principal Investigator of these events.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational products. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents need no longer be retained.

The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor and will provide the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives, and regulatory authorities.

If an Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed on by the Sponsor.

15.5 Confidentiality

All information obtained during the conduct of the study with respect to the subject's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The Investigator must ensure that each subject's anonymity is maintained. On eCRFs and other documents submitted to the Sponsor or the CRO, subjects must not be identified by name. Instead, subjects will only be known by their initials and by the unique subject number allocated to them in order to ensure confidentiality on all study documentation. Subjects will retain this unique number throughout the study. The Investigator will keep a separate log of these codes.

In order to comply with government regulatory guidelines and to ensure subject safety, it may be necessary for the Sponsor and its representative, the CRO personnel, the local research review board, or the US FDA to review subjects' medical records as they relate to this study. Only the subject's unique number on the eCRF will identify him/her, but their full names may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the Sponsor.

Documents that are not for submission to the Sponsor or the CRO (eg, consent forms) will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring by the Sponsor and the CRO and auditing by regulatory authorities. No documents identifying subjects by name will leave the investigative site, and subject identity will remain confidential in all publications related to the study.

16. ADMINISTRATION PROCEDURES

16.1 Regulatory Approval

Seattle Genetics, Inc., or their appointed agents, will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to local country requirements.

16.2 Protocol Amendments

In accordance with ICH Topic E6 (R1) Guideline for GCP, the Investigator should not implement any deviation from or changes to the protocol without agreement by the Sponsor and documented approval from the IRB of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (eg, change in monitor[s] or change of telephone number[s]).

Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the Sponsor. A written amendment must be submitted to the appropriate regulatory authorities and to the IRB assuming this responsibility. The Investigator must await IRB approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to subjects. In these cases, the IRB must be notified within 5 days of the change.

All amendments to the protocol must be approved in writing by both the appropriate regulatory authorities and the IRB, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol.

If, in the judgment of the local IRB, the Investigator and/or Sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the subject, the currently approved written informed consent form will require modification. The modified informed consent form must also be reviewed and approved by the Sponsor, appropriate regulatory authorities, and the IRB. In such cases, repeat informed consent must be obtained from subjects enrolled in the study before participation continues.

16.3 Protocol Adherence and Deviations

The protocol must be read thoroughly, and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the subject requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-Investigator.

In the event of an important protocol deviation due to an emergency, accident, or error, the Investigator or designee must contact the medical monitor at the earliest possible time by telephone. This allows for an early joint decision to be made as to whether or not the subject should continue study treatment. The Investigator, the Sponsor, and the medical monitor will document this decision.

16.4 Study Documentation, Privacy, and Records Retention

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the Investigator until notified by the Sponsor in writing that retention is no longer necessary.

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 the applicable IRB with direct access to original source documents or certified copies.

Records containing patient medical information must be handled in accordance with the requirements of the Health Information Portability and Accountability Act (HIPAA) Privacy Rule and be 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, case report forms 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.

16.5 Publication Policy

The details of the processes of producing and reviewing publications and presentations based on the data from this study will be described in the Clinical Trial Agreement between Seattle Genetics, Inc., and the institution of the Investigator.

16.6 Clinical Study Report

A final clinical study report will be prepared according to the ICH guideline on Structure and Contents of Clinical Study Reports. A final clinical study report will be prepared regardless of whether the study is completed or prematurely terminated.

16.7 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

16.8 Insurance, Indemnity, and Compensation

Seattle Genetics, Inc. undertakes to maintain an appropriate clinical study insurance policy.

Deviations from the study protocol - especially the prescription of a dose other than that scheduled in the study protocol, other modes of administration, other indications, and longer treatment periods - are not permitted and shall not be covered by the statutory subject insurance scheme.

16.9 Discontinuation of the Study

This study may be terminated by the Sponsor. The study may also be terminated prematurely at any time when agreed to by both the Investigator and the Sponsor as being in the best interests of subjects and justified on either medical or ethical grounds. In terminating the study, Seattle Genetics, Inc., the CRO (PRA Health Sciences), and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

16.10 Study Center File Management

The Investigator is responsible for assuring that the Study Center File is maintained. The Study Center File will contain, but will not be limited to, the information listed below:

1. Investigator's Brochure
2. Current, signed version of the protocol and any previous versions of the protocol
3. Protocol amendments (if applicable)
4. Operations manual (if applicable)
5. Current informed consent form (blank) and any previous versions of the informed consent form
6. Curricula vitae of Investigator(s) and sub-Investigator (s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US IND regulations), signed by all Principal Investigators. The names of any sub-Investigators must appear on this form. Investigators must also complete all regulatory documentation as required by ICH GCP and by local or national regulations
7. Documentation of IRB approval of the protocol, the informed consent form, any protocol amendments, and any informed consent form revisions
8. All correspondence between the Investigator, IRB, and the Sponsor/CRO relating to study conduct
9. Laboratory certification(s)
10. Monitoring log
11. Study drug invoices
12. Signature list of all staff completing eCRFs

13. Signature list of all staff completing drug accountability summaries

17. REFERENCE LIST

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18. APPENDICES

18.1 Appendix 1: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

A. Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven

interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    - The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, Sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    - In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

- and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

- Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, Sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, Sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

18.2 Appendix 2: Elements of Informed Consent

ELEMENTS OF INFORMED CONSENT

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

- That the study involves research
- The purpose of the study
- The study treatment(s) and the probability for random assignment to each treatment
- The study procedures to be followed including all invasive procedures
- The subject's responsibilities
- Those aspects of the study that are experimental
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant
- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks
- The compensation and/or treatment available to the subject in the event of study-related injury
- The anticipated prorated payment, if any, to the subject for participating in the study
- The anticipated expenses, if any, to the subject for participating in the study
- That the subject's participation in the study is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential
- That the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study
- The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of study-related injury
- The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated
- The expected duration of the subject's participation in the study
- The approximate number of subjects involved in the study

18.3 Appendix 3: Eastern Cooperative Oncology Group Performance Status

Grade	Criterion
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example light housework or office work.
2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair 50% or more of waking hours.
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair.
5	Death.

18.4 Appendix 4: Common Terminology Criteria for Adverse Events (CTCAE; v 4.03)

The current version of the NCI CTCAE (Version 4.03) can be viewed on-line at the NCI web site:

http://ctep.cancer.gov/reporting/ctc.html

18.5 Appendix 5: Risk Factor Classification for Myelodysplastic Syndromes

18.5.1 The International Prognostic Scoring System

In the IPSS, a score for each patient is derived based on the percent bone marrow blasts, mutation status, and the presence of cytopenias, as follows (a score is assigned for each row, and the total score is the sum of the 3 row scores):

	Score Value				
Prognostic Variable	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	-	11-20	21-30
Karyotype [a]	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

a Good normal, -Y, del(5q), del(20q)
Poor complex (≥3 abnormalities) or chromosome 7 anomalies
Intermediate other abnormalities.

The total score is then used for risk calculation as follows:

Risk Group	Total Score
Low	0
Intermediate-1	0.5-1.0
Intermediate-2	1.5-2.0
High	≥2.5

From: Greenberg P, Cox C, LeBeau MM, et al. International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes. *Blood*. 1997;89 (6):2079-2088.

18.5.2 The World Health Organization (WHO) Classification System

Disease	Blood findings	Bone marrow findings
Refractory anemia (RA)	Anemia No or rare blasts	Erythroid dysplasia only <5% blasts <15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	Erythroid dysplasia only ≥15% ringed sideroblasts <5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods <1 x10^9/L monocytes	Dysplasia in ≤10% of cells in 2 or more myeloid cell lines <5% blasts in marrow No Auer rods <15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods <1 x10^9/L monocytes	Dysplasia in ≥10% of cells in 2 or more myeloid cell lines ≥15% ringed sideroblasts <5% blasts No Auer rods
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias <5% blasts No Auer rods 1 x10^9/L monocytes	Unilineage or multilineage dysplasia 5% to 9% blasts No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias 5% to 19% blasts Auer rods ± <1 x10^9/L monocytes	Unilineage or multilineage dysplasia 10% to 19% blasts Auer rods ±
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias No or rare blasts No Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes <5% blasts No Auer rods
MDS associated with isolated del(5q)	Anemia <5% blasts Platelets normal or increased	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts No Auer rods Isolated del(5q)

From: Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood*. 2002;100:2292-2302.

18.6 Appendix 6: Response Assessment – International Working Group Response Criteria

Category	Response criteria (responses must last at least 4 weeks)
Complete remission Bone marrow:	≤5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb ≥11 g/dL
	Platelets ≥100 x10^9/L
	Neutrophils ≥1.0 x10^9/L†
	Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by ≥50% over pretreatment but still >5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤5% myeloblasts and decrease by ≥ 50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to Marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for >8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following:
	Return to pretreatment bone marrow blast percentage
	Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets
	Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic response	Complete
	Disappearance of the chromosomal abnormality without appearance of new ones
	Partial
	At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with:
	Less than 5% blasts: ≥50% increase in blasts to >5% blasts
	5%-10% blasts: ≥50% increase to >10% blasts
	10%-20% blasts: ≥50% increase to >20% blasts
	20%-30% blasts: ≥50% increase to >30% blasts
	Any of the following:
	At least 50% decrement from maximum remission/response in granulocytes or platelets
	Reduction in Hgb by ≥2 g/dL
	Transfusion dependence
Survival	Endpoints:
	Overall: death from any cause
	Event free: failure or death from any cause
	PFS: disease progression or death from MDS
	DFS: time to relapse
	Cause-specific death: death related to MDS

See footnotes on following page

Deletions to IWG response criteria are not shown.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; PFS, progression-free survival; DFS, disease-free survival.
*Dysplastic changes should consider the normal range of dysplastic changes (modification). (Ramos F, Fernandez-Ferrero S, Suarez D, et al. Myelodysplastic syndrome: a search for minimal diagnostic criteria. *Leuk Res*. 1999;23:283-290)
†Modification to IWG response criteria.
‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

From: Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006; 108(2):419-425.

18.7 Appendix 7: European Organization for Research and Treatment of Cancer (EORTC) Core Module (QLQ-C30)

EORTC website: http://groups.eortc.be/qol/ (Accessed August 31, 2015)

The subject should be instructed to fill out the questionnaires to the best of his/her abilities. The study staff will be responsible for confirming that the subject has completed the questionnaires.

References for the EORTC QLQ-C30 are as follows:

EORTC QLQ C30 (Version 3):

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365 376.

For details of the scoring procedure for the EORTC QLQ-C30:

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, and Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels, Belgium: European Organisation for Research and Treatment of Cancer; 2001.

18.8 Appendix 8: Summary of Amendment 1

RATIONALE:

The protocol was amended to

- To update the definition of the DLT-evaluable population to be those phase 1 patients who completed at least Cycle 1 of treatment or discontinued study treatment because of AEs or for a safety-related reason before having had the opportunity to receive Day 1 of Cycle 2; Cycle 1 of treatment is completed when the patient receives the first dose of azacitidine on Day 1 of Cycle 2. Patients will not have to receive their second dose of vadastuximab talirine to be considered DLT evaluable
- To rename the efficacy-evaluable population as the "modified intent-to-treat (mITT)" population
- Specify certain hematological toxicities that are expected and should not be counted as DLTs
- Exclude patients with prior allo-HCT and those with hypocellular MDS
- More clearly define the entry criteria with regard to bilirubin, specifying values for both direct bilirubin (≤2x ULN) and total serum bilirubin (≤1.5x ULN)
- Allow more flexibility in the IV azacitidine administration by removing the requirement that it be administered by IV push
- Update the dose reduction recommendations to be more specific for MDS
- Modify the description of the bone marrow examination to indicate that biopsy is the preferred method of examination.
- To add a bone marrow biopsy on Cycle 1, Day 28 (+/- 1 week), in the Phase 1 Portion of the study, to assess marrow cellularity in order to distinguish cytopenia due to active MDS from cytopenia due to drug-induced myelosuppression
- Clarify that urinalysis only requires dipstick or microscopy in addition to spot urine protein and creatinine
- Remove erythrocyte sedimentation rate from the list of required inflammatory serologies.
- Update SAE reporting guidance to be consistent with current standards and expected events in MDS
- Remove neuropathy as an AE of special interest
- Remove the requirement for HbA1c at screening; this is not necessary based on accumulating clinical experience with vadastuximab talirine
- To allow serum or urine pregnancy testing
- Change the description of the analysis summaries to match current planning in the statistical analysis plan
- Make minor editorial corrections and clarifications

SUMMARY OF CHANGES:

Note: Editorial and formatting changes are not included below.

Section: Synopsis, Study Design and Methodology, page 5; 9.1.1, Phase 1 Portion – Open-Label Dose Evaluation, page 28; 13.5.3, DLT-Evaluable Population, page 75

Replace:

~~DLT-evaluable subjects are those who complete 2 cycles or discontinue treatment due to study treatment related toxicity before having had the opportunity to receive treatment in Cycle 2.~~

With:

The DLT-evaluable population will include all Phase 1 subjects who have completed at least Cycle 1 of treatment (Cycle 1 of treatment is completed when the patient receives the first dose of azacitidine on Day 1 of Cycle 2) *or* discontinued study treatment because of AEs or for a safety-related reason before having had the opportunity to receive the first dose of azacitidine on Day 1 of Cycle 2.

Section: Synopsis, Study Design and Methodology, page 5; 9.1.1, Phase 1 Portion – Open-Label Dose Evaluation, page 28

Replace:

In the Phase 1 Portion of the study, ~~DLTs will be defined as any hematologic toxicity that delays Cycle 2 by >14 days or any grade 3 or 4 non-hematologic toxicity considered to be related to study treatment.~~

With:

In the Phase 1 Portion of the study, **DLTs will be defined as posttreatment grade 4 neutropenia or grade 4 thrombocytopenia lasting >42 days from the start of therapy, in the absence of evidence of active MDS, or any grade 3 or higher non-hematologic toxicity that is clearly NOT resulting from underlying MDS and is considered related to study treatment, with the exception of:**

a. **Grade 3 allergic reaction, fatigue, asthenia, anorexia, or constipation**
b. **Grade 3 nausea, vomiting, or diarrhea not requiring tube feeding or total parenteral nutrition or hospitalization**
c. **Febrile neutropenia (which resolves with appropriate treatment or marrow recovery), infection, bleeding, or other expected direct complications of cytopenias due to active MDS**

Change:

After 6 DLT-evaluable subjects have had the opportunity to complete **at least Cycle 1 (Cycle 1 of treatment is completed when the patient receives the first dose of azacitidine on Day 1 of Cycle 2)** ~~2 cycles~~ of treatment

Section: Synopsis, Study Design and Methodology, page 5; Synopsis, Study treatments, page 7 (2 places); Table 1, page 30; 9.5.1, Treatments Administered, page 35 (2 places)

Delete (in reference to azacitidine only):

IV ~~push~~

Section: Synopsis, Study Population and Main Criteria for Inclusion/Exclusion, page 6-7; 9.4, Study Population, page 32-33

Replace (Inclusion Criterion 7):

b. serum bilirubin ≤1.5 x upper limit of normal (ULN) or ≤3 x ULN for subjects with Gilbert's disease.

With:

b. direct bilirubin ≤2x upper limit of normal (ULN) and/or total serum bilirubin ≤1.5x ULN (or total serum bilirubin ≤3x ULN for subjects with Gilbert's disease).

Add (Exclusion Criteria 11 and 12):

11. Prior allogeneic hematopoietic stem cell transplant, for any indication.

12. Hypocellular MDS, defined as bone marrow cellularity <30% in subjects ≤60 years old or <20% cellularity in subjects > 60 years old.

Section: Synopsis, Analysis Methods, page 9; 13.6.4.1, Response to Treatment, page 76

Change:

The ORR will be summarized by treatment group and the corresponding ~~95%~~**90%** confidence intervals will be calculated.

Section: 6. Investigators and Study Administrative Structure, page 21

Add:

Central clinical laboratory services will be provided by a central laboratory (refer to the study manual) **for protocol-required hematology and serum chemistry tests; central laboratory results will not be provided to the Investigator**. Additional analyses …

Section: Table 2: Recommended dose modifications for vadastuximab talirine-associated toxicity, page 40

Replace:

Hematologic toxicity in the absence of ~~blasts (CR)~~

With:

Hematologic toxicity in the absence of **active MDS**

Replace (footnote a):

a Blasts are at least 5% in bone marrow by morphology, circulating blasts are present, or there is ~~evidence of extramedullary leukemia~~

With:

a Blasts are at least 5% in bone marrow by morphology, circulating blasts are present, or there is **persisting myelodysplasia contributing to cytopenias**

Section: Table 3: Study Schedule, page 45-46

Add (table body):

Pregnancy test (**serum or** urine) for women of childbearing potential only

Add (to footnote d):

d Day 22-28 in even-numbered cycles until CR, then every 4 cycles thereafter. **In the Phase 1 Portion only, an additional bone marrow biopsy will be performed on Cycle 1, Day 28 (±7 days) to assess bone marrow cellularity. Cycle 1 bone marrow biopsy may be omitted if either a) patient has recovered counts to less than grade 4 cytopenias, ie, absolute neutrophil count (ANC) >500/mcL AND platelet count >25,000/mcL, without transfusion support, by Day 28 of Cycle 1 or b) there is evidence in the peripheral blood of active MDS, eg, circulating blasts.**

Change (footnote e):

e Includes urine dipstick ~~and~~ **or** microscopic analysis, as well as spot urine protein and creatinine.

Delete (footnote g):

g Includes clinical laboratory testing for ~~ESR,~~ CRP, C3, and C4.

Change (footnote p):

p ~~A bone marrow aspirate is sufficient; however, if marrow cannot be aspirated, a biopsy may be conducted.~~

To:

p **Bone marrow examination should be based on a bone marrow biopsy; however, if marrow cannot be biopsied, but aspiration is successful, the aspirate may be used to determine blast count. For subjects in the Phase 1 Portion, at Cycle 1 Day 28, a biopsy is required.**

Section: 10.1, Screening (Day -28 to 1), page 50; 10.3, End of Treatment, page 60

Add:

- **Serum or** urine pregnancy test (women of childbearing potential only)

Section: 10.2.1, Phase 1 Portion, Cycle 1, page 52-53

Add:

- **Day 28 (±7 days):**
    - **Bone marrow biopsy to assess bone marrow cellularity. Cycle 1 marrow biopsy may be omitted if either a) patient has recovered counts to less than grade 4 cytopenias, ie, absolute neutrophil count (ANC) >500/mcL AND platelet count >25,000/mcL, without transfusion support, by Day 28**

of Cycle 1 or b) there is evidence in the peripheral blood of active MDS, eg, circulating blasts.

Note:

A. If the marrow is not hypocellular (total marrow cellularity ≥10%), the patient may proceed to Cycle 2.

B. If the marrow is hypocellular (total marrow cellularity <10%), Cycle 2 should be delayed until count recovery (defined as thrombocytopenia and neutropenia improving to less than CTCAE grade 4: ANC >500/mcL and platelet count >25,000/mcL). If neutrophil count or platelet count have not recovered to less than Grade 4 by Day 42, a repeat marrow should be performed within a week. If the marrow is hypocellular at Day 42, then the subject will have experienced a DLT (posttreatment grade 4 neutropenia or grade 4 thrombocytopenia lasting >42 days from the start of therapy in the absence of evidence of active MDS); if marrow cellularity has recovered to ≥10%, and ongoing cytopenia(s) are attributed to active MDS, then Cycle 2 may be initiated.

Section: 11.3, Bone Marrow Examination, page 62

Change:

Bone marrow examinations for disease assessment at baseline, on treatment, and during follow-up will be performed according to local standards and recorded on the eCRF. After the end of treatment, bone marrow examinations for disease assessment should be performed every 4 months through 24 months after EOT or until initiation of another anticancer treatment, progression, or relapse. Bone marrow examination ~~may~~ be based on a bone marrow ~~aspirate~~; however, if marrow cannot be ~~aspirated, a biopsy~~ may be ~~conducted~~.

To:

Bone marrow examinations for disease assessment at baseline, on treatment, and during follow-up will be performed according to local standards and recorded on the eCRF. After the end of treatment, bone marrow examinations for disease assessment should be performed every 4 months through 24 months after EOT or until initiation of another anticancer treatment, progression, or relapse. Bone marrow examination **should** be based on a bone marrow **biopsy**; however, if marrow cannot be **biopsied, but aspiration is successful, the aspirate** may be **used to determine blast count.**

Add:

In the Phase 1 Portion only, an additional bone marrow biopsy will be performed on Day 28 of Cycle 1 (±7 days). This biopsy is to determine the presence of active MDS in order to determine if any observed cytopenias qualify as DLTs. The Cycle 1 biopsy is not required if there are no cytopenias that need to be assessed (ie, ANC >500/mcL AND platelet count >25,000/mcL, without transfusion support, by Day 28 of Cycle 1) or if there is other evidence of active MDS (eg, circulating blasts in the peripheral blood).

Section: 11.7, Clinical Laboratory Tests, page 67

Add:

For all women of childbearing potential, **serum or** urine pregnancy tests will be performed locally at screening and at EOT.

Delete:

Clinical chemistry: Albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, ferritin, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, uric acid, lipase, **and** amylase~~, and hemoglobin A1c (at screening only)~~.

Add:

Urinalysis: Urine dipstick or microscopic analysis, as well as spot urine protein and creatinine will be performed locally as indicated in Table 3.

Delete:

Inflammatory serologies: ~~Erythrocyte sedimentation rate (ESR),~~ C-reactive protein (CRP), C3, and C4.

Add:

Central laboratory results will not be provided to the study sites.

Section: 12.1.3, Reporting Periods for Adverse Events and Serious Adverse Events, page 72

Delete:

…~~Ongoing non-serious AEs of interest (including, but not limited to, neuropathy) may be followed until resolution, return to baseline, or study closure.~~

Section: 12.1.5, Sponsor Safety Reporting Requirements in the United States, page 73

Change:

~~In this study, the SAEs that do not require individual IND safety reports are disease progression events.~~ **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…

Section: 13.5.4, Modified Intent-to-Treat, page 75

Change (section title):

13.5.4 ~~Efficacy Evaluable~~ **Modified Intent-to-Treat** Population

Change:

The ~~efficacy evaluable~~ **modified intent-to-treat (mITT)** population will include all ITT subjects who received at least 1 dose of study medication (azacitidine or vadastuximab talirine).

Section: 13.6.3, Subject Disposition, page 76

Add:

The number and percent of subjects who discontinue treatment **and withdraw from study** and the reasons for discontinuation **or withdrawal** will be summarized.

Section: 13.6.4.2, Secondary Efficacy Endpoints, page 76

Change:

CR rate will be summarized with ~~95%~~**90%** confidence intervals.

Section: 13.6.8, Additional Data, page 78

Delete:

~~All data collected on the eCRFs will be included in data listings.~~

Section: Global

Replace:

Version ~~01~~, Date ~~24 September 2015~~

With:

Version **02**, Date **18 May 2016**

18.9 Appendix 9: Summary of Changes in Version 3

RATIONALE:

The protocol was amended to

- Clarify the DLT definition (excluding AEs clearly related to azacitidine, and removing the requirement of attribution as related to study treatment from DLT definition)
- Exclude subjects who are candidates for stem cell transplant from the study and to explicitly require a minimum of 30 days between the last dose of vadastuximab talirine and stem cell transplant for those subjects who become candidates during the study
- Add hepatic SAEs (including sinusoidal obstruction syndrome/veno-occlusive disease [SOS/VOD]) as adverse events of special interest
- Add requirements for action by the Independent Data Monitoring Committee (IDMC) to make recommendations based on the occurrence of SOS/VOD
- To exclude subjects with a history of cirrhosis or current alcohol abuse
- To update the dose modifications recommendations based on accumulating clinical experience
- To provide guidance on dose / schedule modifications for patients without adequate hematologic recovery at the end of a cycle, based on count recovery from nadir, marrow response status, and marrow cellularity
- To add vital signs assessments before and after each infusion of vadastuximab talirine (Phase 1 Portion) or blinded study treatment (Phase 2 Portion)
- To update the protocol to make clarifications regarding the use of bone marrow aspirates, as was previously communicated in an administrative letter
- To correct an error in the schedule of events: Collection of weight at Day 1 of each cycle (as was described in the protocol text) had been omitted
- To expand the window for bone marrow examination from "Day 22 to 28" to "Day 22 to 29" for Investigator convenience
- Update the names of the study medical monitors
- Make minor editorial corrections and clarifications

SUMMARY OF CHANGES:

Note: Editorial and formatting changes are not included below.

Section: Cover Page, page 1; 6, Investigators and Study Administrative Structure, page 21

Update the names and contact information for the Medical Monitors:

Replace

[redacted]

With:

[redacted]

Replace

[redacted]

With:

[redacted]

…

[redacted]

Section: Synopsis, Study Design and Methodology, Phase 1 Portion – Open-Label Dose Evaluation, page 5; 9.1.1, Phase 1 Portion – Open-Label Dose Evaluation, page 28-29

Change:

DLTs will be defined as posttreatment grade 4 neutropenia or grade 4 thrombocytopenia lasting >42 days from the start of therapy, in the absence of evidence of active MDS, or any grade 3 or higher non-hematologic toxicity that is clearly NOT resulting from underlying MDS or **azacitidine** ~~and is considered related to study treatment~~, with the exception of:…

…

… will be conducted on Day 22-~~28~~ **29** of even-numbered cycles until CR…

Add:

Subsequently, upon completion of dose escalation, up to 12 more expansion patients may be enrolled (maximum of 24 expansion patients total), at any dose level not previously shown to exceed the MTD, to further characterize safety, PK, and activity.

Section: Synopsis, Study Design and Methodology, Phase 2 Portion – Randomized, Placebo-Controlled, page 5; 9.1.2, Phase 2 Portion – Randomized, Placebo-Controlled, page 29-30

Change:

… will be conducted once between Day 22 and ~~28~~ **29** of even-numbered cycles until CR…

Section: Synopsis, Study Population and Main Criteria for Inclusion/Exclusion, Exclusion Criteria, page 7; 9.4.2, Exclusion Criteria, page 33

Add:

13. Candidates for allogeneic stem cell transplant at the time of screening.
14. History of liver cirrhosis, and / or ongoing alcohol abuse.

Section: Synopsis, Study Design and Methodology, page 5; 9.1, Overall Study Design and Plan, page 28; Table 4, page 45; Table 5, page 47; Table 6, page 49; 10.2, Treatment Period, pp 51-60; 11.4.3, Biomarker Analyses: Bone Marrow Aspirate, page 65

Change:

Day 22 to ~~28~~ OR Days 22-~~28~~

To:

Day 22 to **29** OR Days 22-**29**

Section: Synopsis, Number of Subjects, page 8

Change:

Approximately ~~130~~ subjects; approximately 24 ~~(estimated as 4 cohorts of 6 subjects each)~~ in phase 1 and approximately 106 in phase 2

To:

Approximately **142** subjects; up to **36** in phase 1 and approximately 106 in phase 2

Section: 6, Investigators and Study Administrative Structure, subsection Monitoring and Evaluation Committee(s), page 21

Add:

Conditions requiring IDMC action are provided in Section 13.6.10.

Section: 9.1.3, Study Stopping Criteria, page 31 (new section)

Add:

9.1.3 Study Stopping Criteria

The SMC (Phase 1 Portion) or the IDMC (Phase 2 Portion) will provide recommendations to the Sponsor if either of the following criteria are met:

- **If 5 or more cases of sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) are observed in the interventional (ie, experimental) arm, and the SOS/VOD incidence rate on the interventional arm is >20% of the patients who undergo allo-HCT, and (in the Phase 2 Portion) the rate on the interventional arm is 2 or more fold greater than the rate on the control arm, as determined by the adjudication committee.**
- **If 3 or more cases of severe SOS/VOD are observed in the interventional arm, and the severe SOS/VOD incidence rate on the interventional arm is >10% of the patients who undergo allo-HCT, and (in the Phase 2 Portion) the rate on the interventional arm is 2 or more fold greater than the rate on the control arm, as determined by the adjudication committee.**

The Sponsor will pause enrollment and notify the FDA and other global health authorities, as applicable, if the stopping criteria are met.

Section: 9.5.1.4.2, Overdose, page 39 (new section)

Add:

9.5.1.4.2 Overdose

In the event of an overdose ≥10%, the site should notify the sponsor as soon as they are aware of the overdose.

Section: 9.5.1.4.~~2~~**3**, Dose Modifications, subsection Vadastuximab Talirine, page 39-40

Replace:

Vadastuximab Talirine

Dose delays of any study treatment are permitted. If dosing is delayed for azacitidine, vadastuximab talirine (Phase 1 Portion), or blinded study treatment (Phase 2 Portion), both study treatments should be held and resumed together on the same schedule.

~~Dose reduction of vadastuximab talirine (Phase 1 Portion) or blinded study treatment (Phase 2 Portion) is permitted if a second dose delay is required. The dose will be decreased to the next lower level on the dose-escalation schedule (eg, for a subject enrolled at the 10 mcg/kg dose level, the reduced dose will be 5 mcg/kg). Elimination of up to 2 cycles of vadastuximab talirine or placebo is permitted.~~

Dose modifications to azacitidine are at the discretion of the treating physician and should adhere to the USPI or SMPC, or institutional guidelines/standards.

Azacitidine, vadastuximab talirine, or placebo may be permanently discontinued in the event of unacceptable related toxicity. Subjects will not be considered off study treatment until both study treatments are discontinued.

~~Table 2 describes the guidelines for dose modifications of vadastuximab talirine (Phase 1 Portion) or blinded study treatment (Phase 2 Portion).~~

With:

Vadastuximab Talirine

Table 2 describes guidelines for dose modifications of vadastuximab talirine (Phase 1 Portion) or blinded study treatment (Phase 2 Portion) for toxicity.

Dose delays of any study treatment are permitted. If dosing is delayed for azacitidine, vadastuximab talirine (Phase 1 Portion), or blinded study treatment (Phase 2 Portion), both study treatments should be held and resumed together on the same schedule **except when one agent is omitted during a cycle due to toxicity**.

For patients who have achieved a response to therapy, dose decreases, delays, or dose re-escalation (to original dose level) are permitted at the discretion of the medical monitor and site Investigator. Following achievement of marrow blast clearance to <5% (ie, a CR or marrow CR), patients originally treated with a dose higher than 5 mcg/kg of study drug will receive azacitidine with vadastuximab talirine (Phase 1 Portion) or blinded study treatment (Phase 2 Portion) as continuation therapy at the maintenance dose of 5 mcg/kg in subsequent cycles.

Azacitidine, vadastuximab talirine **(Phase 1 portion)**, or blinded study drug (Phase 2 portion) may be permanently discontinued in the event of unacceptable related toxicity. Subjects will not be considered off study treatment until both study treatments are discontinued.

If subjects become candidates for stem cell transplant after enrollment, vadastuximab talirine must be discontinued at least 30 days prior to stem cell transplant.

Section: Table 2, page 40

Replace:

Table 2: ~~Recommended~~ Dose Modifications for Vadastuximab Talirine-Associated Toxicity

Category	**Event**	**Action**
Hematologic toxicity ~~in the absence of active MDS~~	≥ Grade 3 neutropenia or thrombocytopenia	Cycles of treatment may be delayed up to ~~28~~ days[b] until hematologic recovery is observed. Adequate hematologic recovery is defined as ~~ANC < grade 3, and rising and/or platelets~~ < grade 3 (unsupported). ~~Dose reduction of vadastuximab talirine/blinded study treatment is permitted if a second dose delay is required. The dose will be decreased to the next lower level on the dose escalation schedule. Elimination of up to 2 cycles of vadastuximab talirine or placebo is permitted.~~
Hematologic toxicity with **marrow blasts ≥ 5%**[b] ~~persistent disease~~[a]	≥ Grade 3 neutropenia or thrombocytopenia	Treatment may continue without dose modification
Clinically significant non-hematologic toxicity or asymptomatic non-hematologic laboratory abnormality	≥ Grade 3 event	Treatment delay of up to ~~28~~ days is permitted[b] until resolution of toxicity to < grade 3.

ANC = absolute neutrophil count~~; MDS = myelodysplastic syndrome~~.

~~a Blasts are at least 5% in bone marrow by morphology, circulating blasts are present, or there is persisting myelodysplasia contributing to cytopenias~~

b Delays of >~~28~~ days may be permitted with approval of the medical monitor

With:

Table 2: Dose Modifications for Vadastuximab Talirine-Associated Toxicity

Category	Event	Action
Hematologic toxicity **with marrow blast count <5%**[a]	≥ Grade 3 neutropenia or thrombocytopenia	Cycles of treatment may be delayed up to ~~28~~ **14** days[b] until hematologic recovery is observed. Adequate hematologic recovery is defined as neutropenia and thrombocytopenia **improved to** < grade 3 (unsupported), **OR** **ANC / platelets ≥ [(NADIR COUNT[c]) + [(BASELINE COUNT[d] – NADIR COUNT) x 0.50]** **If hematologic recovery as defined above has not occurred within 14 days of the end of the cycle (by Day 42), omit vadastuximab talirine (Phase 1) or blinded study treatment (Phase 2) from the next cycle, and initiate next dose of azacitidine based on marrow cellularity as defined in Table 3.**
Hematologic toxicity with **marrow blasts ≥ 5%**[b]	≥ Grade 3 neutropenia or thrombocytopenia	Treatment may continue without dose modification until Cycle **5**. At Cycle **5** and beyond, follow action as defined above in hematologic toxicity in the absence of blasts.
Clinically significant non-hematologic toxicity or asymptomatic non-hematologic laboratory abnormality **(with the exception of hepatic toxicity)**	≥ Grade 3 event	Treatment delay of up to **14** days is permitted until resolution of toxicity to < grade 3.
Laboratory evidence of hepatic toxicity (elevation in ALT, AST, or total bilirubin)	**≥ Grade 3 event**	**Treatment delay of up to 14 days is required until resolution of toxicity to ≤ Grade 1 or baseline. If toxicity has not resolved within 14 days, permanently discontinue vadastuximab talirine (Phase 1) or blinded study treatment (Phase 2)**

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase.

a **If cytopenias above grade 3 (eg, ANC <1000/mm^3 or platelets <50 x 10^9/L) are present at Day 28 of a cycle in which no response assessment is required, an 'unscheduled' bone marrow biopsy is required within 14 days of the scheduled end of the cycle (eg, between Day 28 and Day 42). If the bone marrow cellularity is ≤10%, vadastuximab talirine or blinded study treatment will be permanently discontinued. If marrow cellularity is >10%, follow guidance as above.**

b Delays of >**14** days may be permitted with approval of the medical monitor

c **Nadir Count = the lowest count reached during the treatment cycle**

d **Baseline Count = counts prior to Cycle 1 of study treatment**

Section: 9.5.1.4.2, Dose Modifications, subsection Azacitidine, page 39-40

Replace:

~~Dose modification of azacitidine due to toxicity is allowed per institutional standards and according to the USPI at the discretion of the Investigator, including discontinuation of treatment.~~

With:

Dose modifications to azacitidine, including permanent discontinuation due to toxicity, are at the discretion of the treating physician and should adhere to the USPI or SMPC, or institutional guidelines/standards. Recommended schedule

modifications for azacitidine in patients with delayed count recovery and <5% blasts are provided in Table 3.

Section: Table 3, page 41 (new table)

Add:

Table 3: Recommended Scheduled Modifications for Azacitidine in Patients with <5% Blasts and Incomplete Hematologic Recovery at Day 42[a]

Bone Marrow Cellularity:	**>30%**	**15-30%**	**<15%**
Timing of Next Cycle	**Next cycle may begin**	**Delay next cycle until ANC and platelets ≥ [(NADIR COUNT) + [(BASELINE COUNT – NADIR COUNT) x 0.50]**	**Delay next cycle until ANC and platelets ≥ [(NADIR COUNT) + [(BASELINE COUNT – NADIR COUNT) x 0.75]**

a If vadastuximab talirine (Phase 1) or blinded study drug (Phase 2) was omitted during the previous cycle, consider dose reduction of azacitidine to 50% upon initiation of next cycle.

Section: 9.5.3 Prior and Concomitant Therapy, page 41

Change:

Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy, ~~or~~ systemic anti-neoplastic therapy**, or allogeneic stem cell transplant** during the study treatment period.

Section: 10, Study Evaluations by Visit, page 44

Change:

…and ~~a schedule of follow-up assessments is provided in Table 4~~.

To:

…and **schedules of PK, immunogenicity, and biomarker assessments are given in Table 5 and Table 6**.

Section: Table 4 (renumbered), page 45

Separate height and weight into 2 separate rows, with height indicated within 7 days prior to study drug and weight indicated within 7 days prior to study drug and at Day 1 of each cycle.

Change (footnote d):

Day 22~~-28~~**29** in even-numbered cycles until CR, then every 4 cycles thereafter. In the ~~Phase 1 Portion only, an additional bone marrow biopsy will be performed on Cycle 1, Day 28 (±7 days) to assess bone marrow cellularity. Cycle 1 bone marrow biopsy may be omitted if either a) patient has recovered counts to less than grade 4 cytopenias, ie, absolute neutrophil count (ANC) >500/mcL AND platelet count >25,000/mcL, without transfusion support, by Day 28 of Cycle 1 or b) there is evidence in the peripheral blood~~

~~of active MDS, eg, circulating blasts.~~ **If cytopenias above grade 3 (eg ANC <1000/mm3 or platelets <50 x 109/L) are present at Day 28 of a cycle in which no response assessment is required, an 'unscheduled' bone marrow biopsy is required within 14 days of the scheduled end of the cycle (eg, between Day 28 and Day 42) to assess marrow cellularity and blast count, in order to determine if dose / schedule modifications are required in the next cycle.**

Change (footnote p):

For subjects ~~in the Phase 1 Portion, at Cycle 1 Day 28, a biopsy is required~~ **requiring a marrow evaluation to assess cellularity due to cytopenias, a biopsy is required.**

Add:

New row, indicating vital signs assessment on Day 7 of each cycle, with footnote indicator u.

Add (footnote u):

u Before and within 30 minutes after vadastuximab talirine (Phase 1 portion) or blinded study drug (Phase 2 portion) administration.

Section: 10.2.1.1, Cycle 1, page 51; 10.2.1.2, Cycle 2, page 53; 10.2.1.3, Cycle 3, page 54; 10.2.1.4, Cycles ≥4, page 55; 10.2.2.1, Cycle 1, page 56; 10.2.2.2, Cycle 2, page 57; 10.2.2.3, Cycle 3, page 59; 10.2.2.4, Cycles ≥4, page 59 (as a new sub-bullet for Day 7 or 9 pretreatment activities)

Vital signs

Section: 10.2.1.1, Cycle 1, page 52; 10.2.1.2, Cycle 2, page 54 (as a new sub-bullet for Day 7 to 15 or 9 to 17 posttreatment activities)

- **Vital signs (Day 7 or 9 only; within 30 minutes after completing the vadastuximab talirine infusion)**

Section: 10.2.1.3, Cycle 3, page 55; 10.2.1.4, Cycle ≥4, page 56; 10.2.2.1, Cycle 1, page 57; 10.2.2.2, Cycle 2, page 58; 10.2.2.3, Cycle 3, page 59; 10.2.2.4, Cycles ≥4, page 60; (as a new sub-bullet for Day 7 or 9 posttreatment activities)

- **Vital signs (within 30 minutes after completing the vadastuximab talirine infusion)**

Section: 10.2.1.3, Cycle 3, page 55; 10.2.1.4, Cycle ≥4, page 56 (as a new sub-bullet for Day 7 or 9 posttreatment activities)

- **Vital signs (within 30 minutes after completing the vadastuximab talirine infusion)**

Section: Table 5 (renumbered), page 47; Table 6 (renumbered), page 49

Change the spanner head over the last 3 columns of each table to read:

Bone Marrow **Aspirate**

Change:

Day 22~~–28~~ **29**

Section: 10.2.1.2, Cycle 2, Day 1, page 53

Delete:

- ~~Serology laboratory tests (special autoimmune serologies; Section 11.7)~~

Section: 10.2.1.2, Cycle 2, page 54; 10.2.1.4, Cycles ≥4, page 56; 10.2.2.2, Cycle 2, page 58; 10.2.2.4, Cycles ≥4, page 60;

Change:

- Day 22 to~~–28~~**29**:

Section: 10.4, Follow-Up, page 61

Add:

If subjects become candidates for stem cell transplant after enrollment, stem cell transplant should not be performed until at least 30 days after the last dose of vadastuximab talirine.

Section: 11.3, Bone Marrow Examination, page 62

Replace:

~~In the Phase 1 Portion only, an additional bone marrow biopsy will be performed on Day 28 of Cycle 1 (±7 days). This biopsy is to determine the presence of active MDS in order to determine if any observed cytopenias qualify as DLTs. The Cycle 1 biopsy is not required if there are no cytopenias that need to be assessed (ie, ANC >500/mcL AND platelet count >25,000/mcL, without transfusion support, by Day 28 of Cycle 1) or if there is other evidence of active MDS (eg, circulating blasts in the peripheral blood).~~

With:

In addition to response assessment time points, a bone marrow biopsy will be performed between Day 28 and Day 42 of any cycle in which the patient has not achieved hematologic recovery (as defined in Table 2). This biopsy is to determine the blast count and marrow cellularity, in order to determine if dose modification / dose delay is required in the subsequent cycle (Table 2 and Table 3). This biopsy to assess cellularity is not required if counts have recovered (ie, ANC >1000/mm^3 AND platelet count >50,000/mm^3, without transfusion support, by Day 28 of the cycle) or if there are circulating blasts in the peripheral blood (as evidence of active MDS).

Section: 11.4.3, Biomarker Analyses: Bone Marrow **Aspirate**, page 65-66

Add:

A portion of the bone marrow samples **(aspirate)** collected for disease assessment at baseline, for response assessment, and at the time of progression will be preserved for biomarker analyses. **If baseline sample is collected prior to consent, a separate bone**

marrow aspirate will be collected for biomarker analyses. Sample collection and preparation procedures are detailed in the laboratory manual.

Change:

- Day 22~~–28~~ **29** (MDSC; CD33 expression)

…

- Day 22~~–28~~ **29** (MDSC; CD33 expression; mutation profiling)

Section: 11.5, Physical Examination, ECOG Performance Status, ~~and~~ Weight**, and Vital Signs** (revised heading)

Add:

Vital signs (including temperature, heart rate, respiratory rate, and blood pressure) will be assessed at the time points indicated in Table 3 and recorded on the eCRF.

Section: 11.10, Response Assessment, page 68

Change:

…at the end of each even-numbered cycle (Day 22~~–28~~29) until CR,…

Section: 12.1.4, Adverse Events of Special Interest, page 73

Add (new subsection):

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 according to safety reporting requirements. Events of SOS/VOD that occur within 180 days of the last dose of vadastuximab talirine will be reported to the Sponsor. Patients who undergo subsequent allo-HCT in the absence of relapse and additional therapy will be followed for SOS/VOD to 100 days post-transplant.

Section: Global

Replace:

Version 02, Date 18 May 2016

With:

Version **03**, Date **13 April 2017**