



**Protocol Number:** SGN33A-005

**Version:** Amendment 3, 27-March-2017

**Protocol Title:** A randomized, double-blind phase 3 study of vadastuximab talirine (SGN-CD33A) versus placebo in combination with azacitidine or decitabine in the treatment of older patients with newly diagnosed acute myeloid leukemia (AML)

**Study Name:** CASCADE

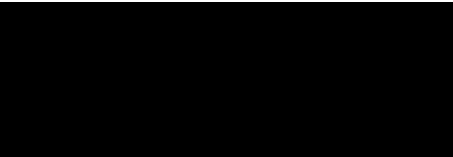
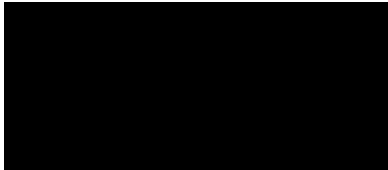
**Investigational Drug:** vadastuximab talirine (SGN-CD33A)

**Phase:** 3

**IND Number:** 116300

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**Sponsor:** Seattle Genetics, Inc.  
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## PROTOCOL SYNOPSIS

<b>Protocol Number</b> SGN33A-005	<b>Product Name</b> vadastuximab talirine
<b>Version</b> Amendment 3; 27-March-2017	<b>Sponsor</b> Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA
<b>Phase</b> Phase 3	

### Protocol Title

A randomized, double-blind phase 3 study of vadastuximab talirine (SGN-CD33A) versus placebo in combination with azacitidine or decitabine in the treatment of older patients with newly diagnosed acute myeloid leukemia (AML)

### Study Objectives

#### Primary

- To compare the composite complete remission (CRc) rate (morphologic complete remission [CR] and morphologic CR with incomplete hematologic recovery [CRi]) between treatment arms
- To compare overall survival (OS) between treatment arms

#### Secondary

- To compare the minimal residual disease-negative remission (MRD-negative CRc) rate between treatment arms
- To evaluate the duration of remission in the 2 treatment arms
- To evaluate event-free survival (EFS) in the 2 treatment arms
- To evaluate leukemia-free survival (LFS) in the 2 treatment arms
- To evaluate the safety profiles in the 2 treatment arms
- To evaluate the time to response in the 2 treatment arms
- To evaluate the 30- and 60-day mortality rates in the 2 treatment arms

#### Additional

- To evaluate the treatment effect of vadastuximab talirine compared to the control group on the change in patient reported outcomes (PRO) and medical resource utilization (MRU)
- To assess the incidence of antitherapeutic antibodies (ATA)
- To assess exploratory markers of clinical outcome and the pharmacodynamics of vadastuximab talirine in combination with a hypomethylating agent (HMA)

### Study Population

The population to be studied includes patients with newly diagnosed, previously untreated, cytologically or histologically confirmed de novo or secondary acute myeloid leukemia (AML), with intermediate or adverse cytogenetic risk (per revised UK Medical Research Council [MRC] classification, ([Grimwade 2010](#)), who are not considered candidates for allogeneic stem cell transplant. Eligible patients must be  $\geq 18$  years of age and have a life expectancy of at least 12 weeks. In addition, patients must be eligible for therapy with either decitabine or azacitidine, have an Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq 2$  (patients age  $\geq 80$  years must have an ECOG performance status of 0 or 1), and have adequate baseline hepatic and renal function.

Patients must not have a history of essential thrombocythemia, polycythemia vera, or primary myelofibrosis, must not have received prior treatment with an HMA or chemotherapy for antecedent myelodysplastic

syndrome (MDS), or have a history of allogeneic stem cell transplant. In addition, patients must not have concurrent active malignancy other than nonmelanoma skin cancer or carcinoma in situ of the following: bladder, stomach, colon, cervix, endometrium, melanoma, or breast. Patients with previous malignancies are eligible if the malignancy has been confined and surgically resected (or treated with other modalities) with curative intent. Any active systemic therapy must have been completed >1 year from enrollment (except for hormonal/anti-hormonal treatment, e.g. breast cancer). Patients are also excluded if they have central nervous system leukemia based on imaging or documented positive cytology in cerebral spinal fluid, or if they have had any uncontrolled Grade 3 or higher viral, bacterial, or fungal infection within 14 days prior to the first dose of study treatment.

### **Number of Planned Patients**

Approximately 540 patients will be randomized in this trial.

### **Study Design**

This is a randomized, double-blind, placebo-controlled phase 3 study designed to compare the CRc rate and OS between patients treated with HMA plus vadastuximab talirine (experimental arm) versus patients treated with HMA plus placebo (comparator arm). Patients will be randomized in a 1:1 manner to one of the study arms. Investigators may select either HMA (azacitidine or decitabine).

Response will be assessed by bone marrow examination and complete blood counts (CBC) between Day 22 to 28 of even numbered cycles until CR or CRi. The response assessment window may be up to Day 42 in the event of a delay in the start of the next cycle of treatment. After CR or CRi, response assessment will continue to be performed by CBC surveillance. In addition, bone marrow examination will be conducted according to the following schedule:

- 2 cycles after initial confirmation of CR or CRi
- At the time of conversion from CRi to CR
- At the time of suspected relapse
- End of treatment (EOT), if not performed within the previous 4 weeks

Patients may continue on study treatment until progression, leukemic recurrence, or unacceptable toxicity, whichever comes first. Patients who achieve stable disease or better should receive a minimum of 4 cycles of study treatment. Progression is defined after 4 or more cycles of treatment as either a >25% absolute rise in the percent of bone marrow blasts from baseline (or a proportional increase of >25% in patients with baseline bone marrow blasts >75%), or appearance of new extramedullary disease. Patients who fulfill the criteria for progression but who are still deriving clinical benefit in the opinion of the investigator may continue on study treatment.

After discontinuation of study treatment, patients will be followed for survival status every 2 months (or more frequently as needed to support analysis of the study endpoints) after EOT until death or study closure, whichever comes first. Patients who have not experienced progression or leukemic recurrence will continue to be assessed for response by CBC surveillance every 2 months through 24 months after EOT, and every 4 months thereafter, until initiation of another anticancer treatment (excluding stem cell transplant and maintenance therapy in the absence of relapse), progression, or leukemic recurrence, whichever comes first.

Two interim analyses for OS are planned: the first interim analysis is to evaluate futility and the second interim analysis is to evaluate the superiority of vadastuximab talirine.

Safety will be monitored over the course of the study by an Independent Data Monitoring Committee (IDMC).

## **Test Product, Dose, and Mode of Administration**

### ***Both Arms***

HMA, either:

- Azacitidine 75 mg/m<sup>2</sup> given subcutaneously (SC) or intravenously (IV) x 7 (7 consecutive days or 5 days on/2 days off/2 days on), every 4 weeks, or
- Decitabine 20 mg/m<sup>2</sup> given IV daily x 5, every 4 weeks

### ***Experimental Arm***

Blinded study treatment: vadastuximab talirine, 10 mcg/kg, every 4 weeks (on the last day of HMA administration) via IV push

### ***Comparator Arm***

Blinded study treatment: placebo, volume equivalent to 10 mcg/kg, every 4 weeks (on the last day of HMA administration) via IV push

## **Duration of Treatment**

Patients may continue on study treatment until progression, leukemic recurrence, or unacceptable toxicity, whichever comes first. Patients who achieve stable disease or better should receive a minimum of 4 cycles of study treatment.

## **Efficacy Assessments**

Anti-leukemic activity will be assessed by routine laboratory tests and bone marrow examinations. Response will be determined according to a modification of the response categorization in the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia ([Cheson 2003](#)).

## **Safety Assessments**

Safety assessments will include the surveillance and recording of adverse events (AEs), physical examination findings, and laboratory tests.

## **Quality of Life Assessments**

Patient-reported outcome (PRO) assessments will be used to obtain quality of life information at protocol-specified timepoints. Two validated tools will be used: the EORTC Quality of Life Questionnaire, QLQ-C30, and the EuroQol 5-dimensions (EQ-5D).

## **Pharmacokinetic, ATA, and Biomarker Assessments**

Validated enzyme-linked immunosorbent assays (ELISA) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays will be used to measure vadastuximab talirine and its associated drug, SGD-1882, respectively. A qualified electrochemiluminescence assay will be used to measure concentrations of ATA in serum. Biomarker assessments may include central assessment of CD33 expression, profiling for somatic mutations or alterations in genes or RNAs commonly altered in hematologic malignancies, and other genes or RNAs potentially associated with disease relapse or resistance to vadastuximab talirine. MRD will be measured. Additional assessments may include measurement of soluble factors such as sCD33 that may be associated with clinical outcome.

## **Statistical Methods**

### ***Stratification***

Patients will be stratified based on the following variables:

- Cytogenetic risk per revised MRC classification
- ECOG performance status
- HMA
- Age

### ***Sample Size Considerations***

There are 2 primary endpoints for this study, CRc rate and OS. To maintain strong control of type I error rate at 0.05, a fallback procedure proposed by Wiens will be used in the testing of the primary endpoints, with an alpha of 0.01 pre-assigned to CRc rate and an alpha of 0.04 pre-assigned to OS.

The sample size was calculated based on maintaining 90% power to test both primary endpoints and to account for 2 planned interim analyses for OS using the O'Brien-Fleming method.

For the primary endpoint of CRc rate, at least 308 patients are required to provide 90% power to detect an improvement in CRc rate from 20% to 40% using a chi-squared test at a significance level of 0.01.

For the primary endpoint of OS, approximately 354 OS events are required with 90% power to detect a hazard ratio of 0.70 (12.9 months median OS in the experimental arm [vadastuximab talirine plus HMA] versus 9 months for the comparator arm [placebo plus HMA]) using a 2-sided log-rank test at an alpha of 0.04.

To provide adequate power for both primary endpoints, a total of 540 patients will be randomized in a 1:1 ratio to either the experimental arm or the comparator arm, assuming an accrual period of approximately 26 months with a slower rate of accrual for the first 6 months, a 12 month follow-up, and a 5% yearly drop-out rate.

### ***Timing of Analyses***

The primary analysis of CRc rate is planned when the following 2 conditions are met: 1) 6 months after 308 patients have been randomized, and 2) approximately 212 OS events have occurred. The estimated duration of the study through the primary analysis of CRc rate is approximately 2 years from randomization of the first patient based on the design assumptions. Only the first 308 patients randomized will be included in the primary analysis of CRc rate. CRc rate will also be analyzed for all randomized patients at the time of the final analysis.

The estimated duration of the study through the final analysis for OS is approximately 3 years from randomization of the first patient based on design assumptions.

Two formal interim analyses for OS are planned in this study. The first interim analysis will take place when approximately 106 OS events have occurred (~30% of the targeted number of events) and will assess the futility of vadastuximab talirine in combination with azacitidine or decitabine.

The second interim analysis for OS will occur in conjunction with the primary analysis of CRc rate. The analysis will be conducted when the following 2 conditions are met: 1) 6 months after 308 patients have been randomized, and 2) approximately 212 OS events have occurred (~60% of the targeted number of events). The interim OS results will be assessed for early stopping for efficacy.

The IDMC will provide recommendations to the sponsor's Data Review Board as to appropriate study direction at the interim analyses.

### ***Analysis Methods***

CRc rate and OS will be analyzed based on the intent-to-treat (ITT) population.

The CRc rate between the experimental and comparator arms will be compared using the Cochran-Mantel-Haenszel test. OS will be analyzed using the Kaplan-Meier method. A stratified log-rank test without adjustments for covariates will be used in the primary evaluation of OS differences between the 2 treatment arms. The hazard ratio along with its confidence intervals will be estimated using an unadjusted stratified Cox model.

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADC	antibody-drug conjugate
AE	adverse event
Allo-SCT	allogeneic stem cell transplant
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
CBC	complete blood count
CCI	Charlson Comorbidity Index
CR	morphologic complete remission
CRc	composite complete remission (CR+CRi)
CRF	case report form
CRi	morphologic complete remission with incomplete blood count recovery
CRi(n)	morphologic complete remission with incomplete neutrophil recovery
CRi(p)/CRp	morphologic complete remission with incomplete platelet recovery
CTFG	Clinical Trial Facilitation Group
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assays
EOT	end of treatment
EQ-5D	EuroQuol 5-dimensions
GCP	good clinical practice
HCT-CI	Hematopoietic Cell Transplantation-Specific Comorbidity Index
HIV	human immunodeficiency virus
HMA	hypomethylating agents
HNSTD	highest non-severely toxic dose
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	Investigational New Drug
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LFS	leukemia-free survival
LTFU	long-term follow up
MCV	mean corpuscular volume
MDR	multidrug resistant
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mLFS	morphologic leukemia-free state
MRC	Medical Research Council

MRD	minimal residual disease
MRU	medical resource utilization
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
OS	overall survival
PBD	pyrrolbenzodiazepine
PCR	polymerase chain reaction
PD	progressive disease
PICC	peripherally inserted central catheter
PR	partial remission
PRO	patient reported outcome
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCT	stem cell transplant
SD	stable disease
Siglec	sialic acid binding sialoadhesin receptor
SmPC	summary of product characteristics
SOS	sinusoidal obstructive syndrome
TTCR	time to complete remission
TLS	tumor lysis syndrome
ULN	upper limit of normal
VOD	veno-occlusive disease
WBC	white blood cell

## 1 INTRODUCTION

### 1.1 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a bone marrow malignancy defined by the dysregulation of differentiation and proliferation of hematopoietic progenitor cells. This results in the uncontrolled proliferation of immature malignant cell blasts and a deficiency in normal blood cells. If untreated, AML generally causes death in weeks to months due to infection, bleeding, or complications related to a large volume of abnormal cells in the vasculature (e.g., disseminated intravascular coagulopathy, endothelial damage). There are approximately 37,000 cases of AML per year across the EU and US (Visser 2012; Siegel 2014). The prognosis for AML heavily depends on factors such as patient age, cytogenetic and molecular abnormalities, and underlying myelodysplasia.

### 1.2 Therapy for AML Patients Unfit for Intensive Induction Chemotherapy

AML is associated with poor survival rates in patients who are not eligible for intensive chemotherapy due to advanced age, medical comorbidities, and/or disease risk factors. Low intensity therapies, such as low dose cytarabine (Burnett 2007), and hypomethylating agents (HMAs), such as decitabine or azacitidine, are frequently employed for this population. Randomized trials in older patients with AML have demonstrated a trend toward improvement in overall survival (OS) for patients treated with either azacitidine or decitabine versus low-dose cytarabine (Fenaux 2010; Kantarjian 2012; Dombret 2015). Outcomes with either of these low-intensity therapies remain suboptimal in this population with very few long-term survivors. The DACO-016 study of decitabine versus treatment choice (low dose cytarabine or best supportive care) in patients  $\geq 65$  years old with newly diagnosed AML (blasts  $\geq 20\%$ ) and poor or intermediate risk cytogenetics, demonstrated an improvement in the remission rate (complete remission [CR] + complete remission with incomplete platelet recovery [CRp]) of 17.8% vs. 7.8% ( $p=0.001$ ) and a nonsignificant increase in median OS of 7.7 months vs. 5 months ( $p=0.108$ ) (Kantarjian 2012). The AML-001 trial of azacitidine compared to conventional care regimens (including supportive care, low dose cytarabine, or intensive chemotherapy) in patients  $\geq 65$  years old with newly diagnosed AML (blasts  $\geq 30\%$ ) and poor or intermediate risk cytogenetics, demonstrated a CR+ complete remission with incomplete blood count recovery (CRi) rate of 27.8% vs. 25.1% ( $p=0.5384$ ) and a median OS of 10.4 month vs. 6.5 month ( $p=0.1009$ ) (Dombret 2015).

Although intensive chemotherapy-based therapies are available, these approaches in older, unfit patients with AML are associated with increased treatment-related mortality and inferior outcomes compared to younger, fit patients (Juliussen 2009; Kantarjian 2010). Deaths during initial treatment with intensive regimens have been reported in as many as 20 to 30% of patients (Klepin 2013), treatments require prolonged hospitalizations (Roboz 2012), and the 5-year OS is approximately 10%. The AML-001 trial of azacitidine in this patient population has demonstrated that the overall survival rate with azacitidine was equivalent, if not superior, to intensive chemotherapy (Dombret 2015). Retrospective observational studies have also demonstrated that survival rates are equivalent in older

patients when treated with HMA compared to standard anthracycline/cytarabine-based regimens studies (Quintas-Cardama 2012; Gupta 2015).

Given the lack of safe and effective therapeutic options for primarily older adults with AML who are not candidates for intensive induction chemotherapy, there continues to be a significant unmet medical need for improved treatment options in this patient population.

### 1.3 CD33

CD33, also known as Siglec-3 or gp67, is a 67 kilodalton glycosylated transmembrane protein of the sialic acid binding sialoadhesin receptor (Siglec) family (von Gunten 2008; Jandus 2011). Signaling through CD33 has been reported to mediate inhibitory signals that regulate intracellular calcium mobilization (Ulyanova 1999), cell adhesion (Taylor 1999), apoptosis of leukemic cells (Vitale 2001), myeloid cell maturation (Ferlazzo 2000), as well as production of cytokines (Sutherland 2009).

The CD33 antigen is present on the surface of malignant cells in the majority of patients with AML. As described in detail in the vadastuximab talirine Investigator's Brochure, CD33-targeted agents have been investigated as treatments for AML with modest success. For example, efforts to integrate the CD33-targeted antibody drug conjugate (ADC) gentuzumab ozogamicin as part of frontline AML therapy have demonstrated improvement in event-free and/or overall survival in subsets of patients (Burnett 2011; Delaunay 2011; Burnett 2012; Castaigne 2012). Taken together, these previous data help confirm the validity of CD33 as a drug target, but suggest that an improved ADC with a favorable safety and toxicity profile is desirable (Jurcic 2012).

### 1.4 Vadastuximab Talirine

Vadastuximab talirine (also referred to as SGN-CD33A) is an ADC consisting of 3 functional subunits: 1) an anti-CD33 antibody with an engineered cysteine residue in position 239 of each heavy chain (h2H12ec), 2) a DNA cross-linking pyrrolobenzodiazepine (PBD) dimer drug (SGD-1882), and 3) a protease-cleavable linker that covalently attaches SGD-1882 to h2H12ec.

[REDACTED]

## 1.5 Rationale for Vadastuximab Talirine in Combination with Hypomethylating Agents

Hypomethylating agents (HMAs) reduce the methylation of genes through covalent interactions with DNA methyltransferase enzymes (Lyko 2005), resulting in the increased expression of epigenetically silenced genes. Gene demethylation and disruption of the genetic machinery by azacitidine or decitabine have been reported to promote cell differentiation and to exert cytotoxic effects on tumor cells (Flotho 2009; Hollenbach 2010). Epigenetic priming with HMAs has also been shown to sensitize resistant tumor cells to cytotoxic drugs (Plumb 2000; Niitsu 2006; Qin 2007).

In preclinical studies combining vadastuximab talirine with HMAs (azacitidine and decitabine), enhanced activity was demonstrated in multidrug resistant (MDR)-positive AML models (Sutherland 2014). Enhanced tumor cell killing in these models was associated with synergism in the activation of the DNA damage sensory and apoptosis pathways. Furthermore, increased exposure of AML cells to HMAs appeared to modestly upregulate cell surface expression of CD33 and increase incorporation of PBD dimer into DNA (Sutherland 2015). The combination of HMAs with vadastuximab talirine may exact a greater burden on the DNA repair pathway in leukemic cells, enhancing the processes leading to apoptosis and cell death.

The clinical safety and activity of vadastuximab talirine has been evaluated in a phase 1 first-in-human study (Study SGN33A-001), with 10 mcg/kg identified as the recommended dose in combination with decitabine or azacitidine. In the combination cohort of this phase 1 study (N=24), the regimen was generally well tolerated with a low early mortality rate observed. At the time of an interim analysis (July 2015), Grade 3 or higher adverse events (AEs) reported in >20% of patients were febrile neutropenia (46%), anemia (25%), neutropenia (25%), and thrombocytopenia (21%). Other treatment-emergent AEs regardless of relationship to study treatment reported in >20% of patients were nausea (29%), decreased appetite (25%), and constipation (21%). Fifteen of the 23 efficacy evaluable patients (65%) achieved CR (5 patients, 22%) or CRi (10 patients, 43%) (Fathi 2015). Complete remissions were observed in patients with adverse risk factors.

A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects is provided in the Investigator's Brochure.

## **2 OBJECTIVES**

### **2.1 Primary Objectives**

- To compare the composite complete remission (CRc) rate (morphologic complete remission [CR] and morphologic CR with incomplete hematologic recovery [CRi]) between treatment arms
- To compare overall survival (OS) between treatment arms

### **2.2 Secondary Objectives**

- To compare the minimal residual disease-negative remission (MRD-negative CRc) rate between treatment arms
- To evaluate the duration of remission in the 2 treatment arms
- To evaluate event-free survival (EFS) in the 2 treatment arms
- To evaluate leukemia-free survival (LFS) in the 2 treatment arms
- To evaluate the safety profiles in the 2 treatment arms
- To evaluate the time to response in the 2 treatment arms
- To evaluate the 30- and 60-day mortality rates in the 2 treatment arms

### **2.3 Additional Objectives**

- To evaluate the treatment effect of vadastuximab talirine compared to the control group on the change in patient reported outcomes (PRO) and medical resource utilization (MRU)
- To assess the incidence of antitherapeutic antibodies (ATA)
- To assess exploratory markers of clinical outcome and the pharmacodynamics of vadastuximab talirine in combination with a hypomethylating agent (HMA)

### **2.4 Endpoints**

#### **2.4.1 Primary Efficacy Endpoints**

- CRc rate
- OS

#### **2.4.2 Secondary Endpoints**

The secondary endpoints are:

- MRD-negative CRc rate
- Duration of remission

- EFS
- LFS
- Type, incidence, severity, seriousness, and relatedness of adverse events
- Laboratory abnormalities
- Time to CR or CRi
- Mortality rates at Day 30 and Day 60 post the first study treatment

### **2.4.3 Additional Endpoints**

- Change from baseline in PRO
- MRU based on the number of medical care encounters
- Incidence of ATA to vadastuximab talirine
- Biomarkers of pharmacodynamic effects
- Exploratory markers of clinical activity

## **3 INVESTIGATIONAL PLAN**

### **3.1 Summary of Study Design**

This is a randomized, double-blind, placebo-controlled, phase 3 study designed to compare the CRc rate and OS between patients treated with HMA plus vadastuximab talirine (experimental arm) versus patients treated with HMA plus placebo (comparator arm). Approximately 540 patients will be randomized in a 1:1 manner to one of the study arms (~270 patients per arm). Investigators may select either HMA (azacitidine or decitabine; see Section 5.1 for details).

Response will be assessed by bone marrow examination and complete blood counts (CBC) conducted between Day 22 to 28 of even-numbered cycles until CR or CRi. The response assessment window may be up to Day 42 in the event of a delay in the start of the next cycle of treatment. After CR/CRi, response assessment will continue to be performed by CBC surveillance. In addition, bone marrow examination will be conducted according to the following schedule:

- 2 cycles after initial confirmation of CR or CRi
- At the time of conversion from CRi to CR
- At the time of suspected relapse
- EOT (if not performed within the previous 4 weeks)

Patients may continue on study treatment until progression, leukemic recurrence, or unacceptable toxicity, whichever comes first. Patients who achieve stable disease or better

should receive a minimum of 4 cycles of study treatment. Progression is defined after 4 or more cycles of treatment as either a >25% absolute rise in the percent of bone marrow blast from baseline (or a proportional increase of >25% in patients with baseline bone marrow blasts >75%) or appearance of new extramedullary disease. Patients who fulfill the criteria for progression but who are still deriving clinical benefit in the opinion of the investigator may continue on study treatment.

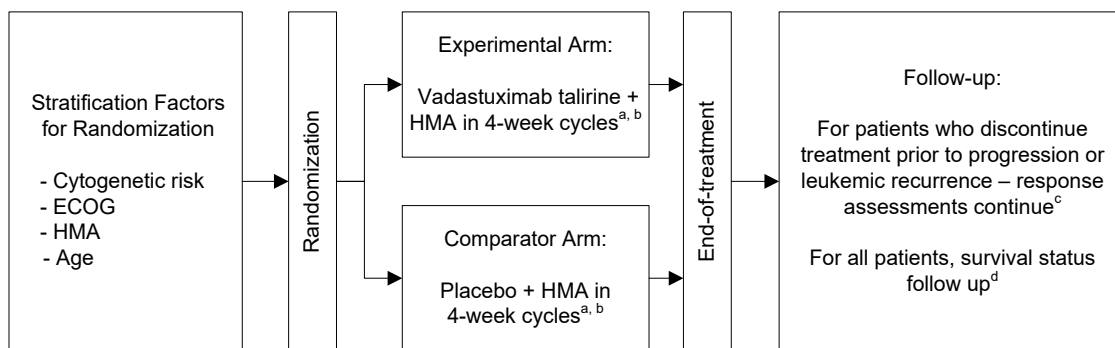
After discontinuation of study treatment, patients who have not experienced progression or leukemic recurrence will continue to be assessed for response by CBC surveillance every 2 months through 24 months after the end-of-treatment (EOT), and every 4 months thereafter, until initiation of another anticancer treatment (excluding SCT and maintenance therapy in the absence of relapse), progression, or leukemic recurrence, whichever comes first. For all patients, survival status follow up will take place every 2 months (or more frequently as needed to support analysis of the study endpoints) after EOT until death or study closure, whichever comes first.

Two interim analyses for OS are planned: the first interim analysis is to evaluate futility and the second interim analysis is to evaluate the superiority of vadastuximab talirine (see Section 9.3.10).

Safety, including SAEs and early mortality, will be monitored over the course of the study by an Independent Data Monitoring Committee (IDMC).

A study schema is presented in Figure 1.

**Figure 1: Study Design**



- a Open-label treatment with HMA administered in combination with blinded vadastuximab talirine or placebo. HMA = either azacitidine 75 mg/m<sup>2</sup> SC or IV x 7, every 4 weeks or decitabine 20 mg/m<sup>2</sup> IV x 5, every 4 weeks.
- b Treatment until progression or leukemic recurrence. Response assessments between Day 22–28 of even-numbered cycles until CR or CRi. After CR or CRi, response will continue to be evaluated by CBC every cycle; bone marrow examinations will be performed as described in Section 6.
- c Response assessed by CBC every 2 months through 24 months after EOT, and every 4 months thereafter, until initiation of another anticancer treatment (excluding stem cell transplant and maintenance therapy in the absence of relapse), progression, or leukemic recurrence, whichever comes first.
- d Every 2 months after EOT (or more frequently as needed to support analysis of the study endpoints) until death or study closure, whichever comes first.



### 3.1.1 Study Stopping Criteria

The Sponsor will pause enrollment and notify the FDA, and other global health authorities as applicable, if the stopping criteria are met. The IDMC will provide recommendations to the Sponsor if either of the following criteria are met:

- 

[REDACTED]

- 

[REDACTED]

### 3.2 Discussion and Rationale for Study Design

Non-intensive therapies, such as the HMAs decitabine and azacitidine, are frequently employed for patients with AML who are not candidates for intensive induction chemotherapy or allogeneic SCT, although response rates and median survival remain suboptimal in this population. HMAs are considered a standard of care option in patients for whom a low intensity therapy is deemed appropriate. Clinical practice guidelines support their use in this setting, and randomized phase 3 trials have shown these agents to have similar efficacy compared to other recommended low intensity therapies such as subcutaneous low dose cytarabine (Dohner 2010; Kantarjian 2012; Dombret 2015).

Patients with intermediate and adverse risk AML who are not considered candidates for allogeneic transplant define a population in which low response rates and high mortality rates have been observed with intensive chemotherapy regimens. Less than 10% of older patients are cured with traditional chemotherapeutic regimens (Appelbaum 2006; Buchner 2009). Retrospective observational studies have demonstrated that survival rates are equivalent in these older patients when treated with HMAs compared to standard anthracycline/cytarabine-based regimens (Quintas-Cardama 2012; Gupta 2015). In addition, a large prospective randomized study demonstrated that in the proposed patient population, the overall survival with azacitidine was equivalent, if not superior, to intensive chemotherapy (Dombret 2015). Patients with favorable risk AML who have potentially chemotherapy-sensitive karyotypes will be excluded from this trial. It is intended that the study population will primarily be older patients who have been shown to benefit from low-intensity therapies such as HMAs, but are medically unfit and/or unwilling to receive standard intensive induction chemotherapy. Historical data show that within the older AML population, outcomes are worse in the subset of patients who are age 80 years and older with poor performance status (Kantarjian 2010; Oran 2012). Age  $\geq 80$  years and a high degree of comorbidity were associated with an increased risk of early death and shorter median overall survival

regardless of therapy received, including HMAs. Therefore, patients age 80 and older will be required to have an ECOG performance status of 0 or 1.

The randomized trial design of the current study includes the opportunity for the investigator to select from either HMA (decitabine or azacitidine) prior to patient randomization. Both decitabine and azacitidine have very similar mechanisms of action, whereby they are incorporated into DNA leading to DNA methyl-transferase inhibition, DNA hypomethylation, and induction of DNA damage.

CD33 is expressed on leukemic blasts in approximately 90% of patients with AML (Pollard 2012; Ehninger 2014; Krupka 2014). Because all patients enrolled on this study will receive an HMA, which is standard of care for AML regardless of CD33 expression, documentation of CD33 expression will not be required to enroll on this trial.

Remission will be evaluated by investigator assessment with local pathology according to a modification of the response categorization in the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia (Cheson 2003); see Appendix E. The blinded, randomized design of this study ensures the robustness of investigator-assessed remission status.

### 3.2.1 Method of Assigning Patients to Treatment Groups

Following informed consent and screening assessments, patients will be randomly assigned to study treatment in a 1:1 ratio. Randomization procedures are detailed in the Study Manual.

Stratified block randomization will be performed centrally. Patients will be stratified by the following factors:

- Cytogenetic risk per revised UK Medical Research Council (MRC) classification (intermediate versus adverse; see Appendix D). Local assessment of cytogenetic risk will be used for eligibility and stratification.
- Eastern Cooperative Oncology Group (ECOG) performance status (0–1 versus 2)
- HMA (azacitidine versus decitabine)
- Age (<75 years versus ≥75 years)

### 3.2.2 Rationale for Selection of Doses

In the first-in-human study (Study SGN33A-001), a 10 mcg/kg dose of vadastuximab talirine was selected for evaluation in combination with HMAs because it was the highest dose where no dose-limiting toxicities (DLTs) were observed in the monotherapy cohorts. It also represented the no observed adverse effect level (NOAEL) and 1/6th of the highest non-severely toxic dose (HNSTD) in the single-dose monkey toxicology study. In the cohort of 24 AML patients who received combination therapy in Study SGN33A-001, tolerable myelosuppression was observed, no DLTs were noted, and there has been no clinically-significant off-target toxicity. At the time of an interim analysis (July 2015), the 30- and 60-day mortality rates were 0% and 4%, respectively, with no treatment-related

deaths reported. The observed remission rate of 65% was more than double the historical rate associated with HMA monotherapy in this patient population ([Fathi 2015](#)).

The clinical safety data observed in the phase 1 dose-escalation study of vadastuximab talirine support 10 mcg/kg every 4 weeks as the dose and schedule in combination with an HMA. Dose reductions of blinded study treatment to 5 mcg/kg are permitted (see [Section 5.2.3](#)). The primary rationale for selection of the combination dose level is the observed activity balanced with the acceptable safety and tolerability profile.

### **3.2.3 Blinding**

Maintaining the blind of the study is crucial for achieving the study objectives. Investigators, patients, and the sponsor will be blinded to treatment assignments, unless otherwise specified in the Study Manual.

Prior to study closure, unblinding a patient's treatment assignment must be limited to emergency circumstances where knowledge of the treatment assignment would affect decisions regarding the management of the patient. In the event of such an emergency circumstance, a formal unblinding procedure, carried out by a third party organization, will be followed to allow the investigator to immediately access a patient's treatment assignment (see Study Manual). Information on study treatment assignment should not be distributed to any other personnel involved in the clinical trial. In the event of any emergency unblinding, Seattle Genetics is to be notified within 24 hours of the occurrence.

## **4 STUDY POPULATION**

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

### **4.1 Inclusion Criteria**

1. Patients with newly diagnosed, previously untreated, cytologically or histologically confirmed de novo or secondary AML according to WHO classification (except for acute promyelocytic leukemia [APL]).
2. Age  $\geq 18$  years.
3. Life expectancy of at least 12 weeks.
4. Patient is eligible for therapy with either decitabine or azacitidine.
5. For patients  $< 80$  years, an ECOG performance status  $\leq 2$  ([Appendix C](#)). Patients  $\geq 80$  years must have an ECOG performance status of 0 or 1.
6. The following baseline laboratory data:
  - White blood cell (WBC) count  $< 30,000/\mu\text{L}$ ; use of hydroxyurea to control WBC is acceptable.

- Serum bilirubin  $\leq 1.5$  x upper limit of normal (ULN) or  $\leq 3$  x ULN for patients with Gilbert's disease, or direct bilirubin  $\leq 2$  x ULN if total bilirubin is abnormal.
  - Serum creatinine  $\leq 2.5$  x ULN and estimated creatinine clearance  $\geq 30$  mL/min.
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)  $\leq 3$  x ULN.
7. Female patients (for those of childbearing potential as defined in Section 4.3), the following stipulations apply:
- a. Must have a negative serum or urine pregnancy test (minimum sensitivity 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [ $\beta$ -hCG]) result within 7 days prior to the first dose of study treatment. Females with false positive results and documented verification that the patient is not pregnant are eligible for participation.
  - b. Must agree not to try to become pregnant during the study and for at least 6 months after the final dose of study drug administration.
  - c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 6 months after the final dose of study drug administration.
  - d. If heterosexually active, must consistently use 2 highly effective methods of birth control (as defined in [Appendix G](#)) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug administration.
8. Male patients under the following conditions:
- a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 6 months after the final study drug administration.
  - b. If heterosexually active with non-pregnant, pregnant, or breastfeeding partner, must consistently use 2 highly effective methods of birth control (as defined in [Appendix G](#)) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug administration.
9. Patients must provide written informed consent.

## 4.2 Exclusion Criteria

1. AML associated with favorable risk karyotypes including inv(16), t(8;21), t(16;16), or t(15;17).
2. Patients who are medically fit and willing to receive standard intensive induction chemotherapy.

3. Patients who are candidates for allogeneic stem cell transplant at the time of enrollment.
4. Patients with a history of one of the following myeloproliferative neoplasms: essential thrombocythemia, polycythemia vera, and primary myelofibrosis.
5. Received prior treatment with HMA or chemotherapy for antecedent MDS. Prior hydroxyurea or 6-mercaptopurine is permitted, as is prior lenalidomide treatment for MDS.
6. History of allogeneic stem cell transplant.
7. History of clinically significant chronic liver disease (e.g. liver cirrhosis) and/or ongoing alcohol abuse.
8. Patients with supplemental oxygen requirement or resting oxygen saturation of <90%.
9. Concurrent active malignancy other than nonmelanoma skin cancer or carcinoma in situ of the following: bladder, stomach, colon, cervix, endometrium, melanoma, or breast. Patients with previous malignancies are eligible if the malignancy has been confined and surgically resected (or treated with other modalities) with curative intent. Any active systemic therapy must have been completed >1 year from enrollment (except for hormonal/anti-hormonal treatment, e.g. breast cancer).
10. Central nervous system leukemia based on imaging or documented positive cytology in cerebral spinal fluid.
11. Any uncontrolled Grade 3 or higher (per NCI 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.
12. Patients with any of the following:
  - Known positive hepatitis B polymerase chain reaction (PCR) assay who have also tested positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody; patients with a negative PCR assay are permitted with appropriate antiviral prophylaxis.
  - Known or suspected active hepatitis C infection (positive by PCR or on antiviral therapy within the last 6 months).
  - Known human immunodeficiency virus (HIV) infection.
13. 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 cardiac symptoms consistent with New York Heart Association (NYHA) Class III-IV within 6 months prior to the first dose of study treatment (see [Appendix F](#)).
14. Current therapy with other systemic anti-neoplastic or investigational agents, with the exception of hydroxyurea.

15. Females who are breastfeeding.
16. Known hypersensitivity to any excipient contained in the drug formulation of any study treatment.
17. Significant history of pulmonary, renal, neurologic, psychiatric, endocrine, metabolic, immunologic, hepatic, cardiovascular disease, or any other condition which, in the opinion of the investigator, would adversely affect participation in this study, compromise patient safety or interfere with data interpretation.

### **4.3 Childbearing Potential**

A woman of childbearing potential is any female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological, physiological, or pharmacological causes.

### **4.4 Removal of Patients From Therapy or Assessment**

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

#### **4.4.1 Discontinuation of Study Drug**

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

- Progressive disease (including leukemic relapse/recurrence)
- Adverse event (AE)
- Investigator decision
- Patient decision, Non-AE
- Study termination by sponsor
- Other, Non-AE

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent.

#### **4.4.2 Patient Withdrawal From Study**

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

- Patient withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

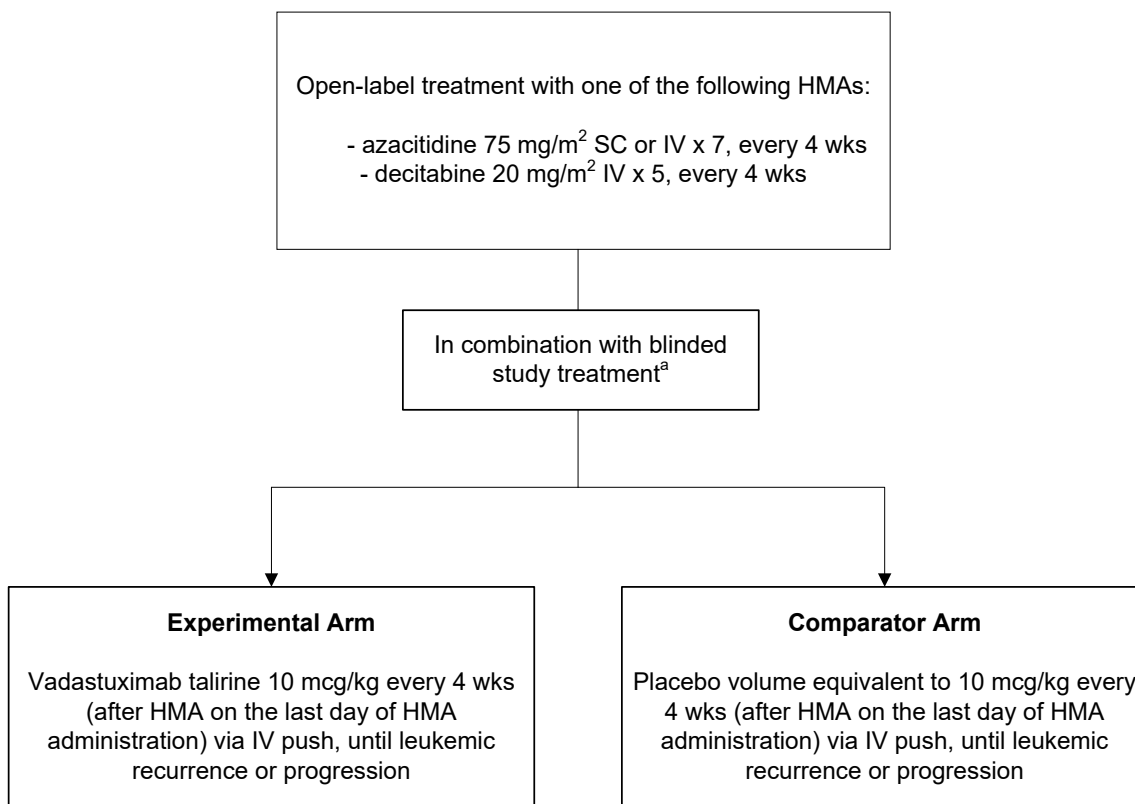
## 5 TREATMENTS

### 5.1 Treatments Administered

Patients in this study will be treated with HMA (azacitidine or decitabine) administered in combination with either vadastuximab talirine (experimental arm) or placebo (comparator arm); see [Figure 2](#).

Investigators may choose either HMA for the majority of the study. However, to ensure balanced proportions of patients receive either decitabine or azacitidine for analysis of the primary endpoint, there may be certain periods during which the specific HMA will be assigned.

**Figure 2: Study Treatments**



<sup>a</sup> Randomized in a 1:1 ratio (vadastuximab talirine: placebo)

### 5.2 Investigational Study Drug

Investigational study drug (vadastuximab talirine or placebo) will be supplied in a blinded manner. Detailed information describing the preparation, administration, and storage of study treatment is located in the Pharmacy Binder.

#### 5.2.1 Description

Vadastuximab talirine and placebo are supplied as a sterile, preservative-free, lyophilized cake or powder for reconstitution for IV administration and are supplied by Seattle Genetics

in single-use amber glass vials. Each vial of vadastuximab talirine contains vadastuximab talirine, [REDACTED]

## 5.2.2 Dose and Administration

The patient will be randomized to either the experimental arm or the comparator arm within 1 business day prior to the first dose of HMA.

Dosing is based on patient actual body weight (to the nearest tenth of a kilogram) obtained according to the institutional standard; however, doses must be adjusted for patients who experience a  $\geq 10\%$  change in weight from baseline. **An exception to weight-based dosing is made for patients weighing greater than 100 kg; doses will be based on 100 kg for these individuals (the maximum dose for this study is 1000 mcg per single 10 mcg/kg dose).**

The dose of study treatment is 10 mcg/kg every 4 weeks (after HMA on the last day of HMA administration) via IV push. It is recommended that study treatment is administered via central venous access port (e.g., peripherally inserted central catheter [PICC], Hickman line, or similar according to institutional standard). However, if study treatment 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 in “Preventing and Managing Vesicant Chemotherapy Extravasations” ([Schulmeister 2010](#)).

Depending on the lot of study treatment supplied, a sterile 0.2  $\mu\text{m}$  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.

## 5.2.3 Dose Modifications

Dose modifications (delays, reductions, or eliminations) of blinded study treatment are at the discretion of the investigator; see [Table 1](#) for required dose modifications. Cycles of blinded study treatment may be delayed for hematologic toxicity in the absence of leukemia. A dose reduction of blinded study treatment to 5 mcg/kg is permitted if a second dose delay is required. After dose reduction, a delay of up to 56 days is permitted before resuming blinded study treatment. Consider bone marrow evaluation in the setting of prolonged cytopenias.



**Table 1: Dose modifications for blinded study treatment-associated toxicity**

Category	Event	Action
Hematologic toxicity in the absence of leukemia (CR, CRi, morphologic leukemia-free state [mLFS]; see <a href="#">Appendix E</a> )	≥ Grade 3 neutropenia or thrombocytopenia	Cycles of blinded study treatment must be delayed up to 28 days <sup>b</sup> 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 blinded study treatment to 5 mcg/kg is permitted after any dose delay, and is required if a second dose delay occurs. Treatment must be discontinued for delays of >56 days after dose reduction, unless approved by the medical monitor.
Hematologic toxicity with persistent leukemia <sup>a</sup>	≥ Grade 3 neutropenia or thrombocytopenia	Blinded study treatment may continue without dose modification.
Non-hematologic toxicity or non-hematologic laboratory abnormality (with the exception of hepatic toxicity)	≥ Grade 3 event	Treatment delay of up to 14 days is required <sup>b</sup> 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, must permanently discontinue blinded study treatment.

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

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

HMA dose modifications are at the discretion of the treating physician and should adhere to the HMA package insert or Summary of Product Characteristics (SmPC) or institutional guidelines/standards. If dosing is delayed for either blinded study treatment or HMA, both should be held and resumed together on the same schedule.

Blinded study treatment or HMA treatment may be permanently discontinued in the event of unacceptable treatment-related toxicity. Patients will not be considered off treatment until both blinded study treatment and HMA have been discontinued.

## 5.2.4 Storage and Handling

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

Chemical and physical stability of the reconstituted drug product has been demonstrated for 24 hours at 2–8°C, protected from light. However, the 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 standard, at the time of use. The prepared dosing solution (reconstituted

drug product or drug product dilution) may be kept for up to 4 hours at room temperature in the amber vial.

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

Do not shake reconstituted or diluted study treatment.

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

Drug accountability instructions are provided in the Pharmacy Binder.

### **5.2.5 Packaging and Labeling**

Refer to the Pharmacy Binder for information regarding packaging and labeling.

### **5.2.6 Preparation**

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

Study treatment must be reconstituted before administration. The reconstituted drug product may be further diluted depending on the dose level. Detailed drug preparation instructions are provided in the Pharmacy Binder.

## **5.3 Azacitidine and Decitabine**

### **5.3.1 Description**

Azacitidine is a pyrimidine nucleoside analog of cytidine. It is a white to off-white solid. Branded or generic equivalent may be used. It is recommended that azacitidine is administered subcutaneously (SC) unless contraindicated, in which case intravenous (IV) administration is permitted. Azacitidine is supplied in a sterile form for reconstitution for subcutaneous injection or reconstitution as a solution with further dilution for IV infusion. Vials contain 100 mg of azacitidine and 100 mg mannitol as a sterile lyophilized powder.

Decitabine is an analogue of the natural nucleoside 2'-deoxycytidine. Decitabine is a fine, white to almost white powder with the molecular formula of C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>4</sub> and a molecular weight of 228.21. Branded or generic equivalent may be used. Decitabine for injection is a white to almost white sterile lyophilized powder supplied in a clear colorless glass vial. Each 20 mL, single dose, glass vial contains 50 mg decitabine, 68 mg monobasic potassium phosphate (potassium dihydrogen phosphate) and 11.6 mg sodium hydroxide.

### **5.3.2 Method of Procurement**

In the US, azacitidine and decitabine will be supplied by the study site and billed to patients and/or their third-party payer (insurance, a healthcare provider, or applicable government

program). In countries outside of the US, supplies will be re-labeled to meet country-specific regulatory requirements and supplied by the sponsor.

### **5.3.3 Dose and Administration**

Refer to the azacitidine and decitabine package inserts or SmPC for complete instructions for dosing and administration. The dose of azacitidine is 75 mg/m<sup>2</sup> SC or IV x 7 (7 consecutive days or 5 days on/2 days off/2 days on), every 4 weeks. The dose of decitabine is 20 mg/m<sup>2</sup> IV daily x 5, every 4 weeks. Dose modifications for HMAs are discussed in Section 5.2.3.

### **5.3.4 Storage and Handling**

Refer to the azacitidine and decitabine package inserts for appropriate storage and handling instructions.

### **5.3.5 Packaging and Labeling**

Refer to the azacitidine and decitabine package inserts for packaging and labeling information.

### **5.3.6 Preparation**

Preparation of azacitidine and decitabine should be according to the appropriate package inserts and in adherence to institutional standards.

## **5.4 Required Premedication and Postmedication**

There are no required pre- or postmedications for any component of study treatment.

## **5.5 Concomitant Therapy**

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related adverse event should be recorded from the time of informed consent.

### **5.5.1 Required Concomitant Therapy**

None.

### **5.5.2 Allowed Concomitant Therapy**

Antimicrobial prophylaxis measures are strongly recommended, per institutional standard of care; decisions regarding use and choice of antibiotics should be made by the individual institutions based on the prevailing organisms and their drug resistance patterns (de Naurois 2010; Freifeld 2011; Flowers 2013). The use of myeloid growth factors are considered appropriate supportive care per the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines (Smith 2006; Fey 2013) and are strongly recommended as primary and/or secondary prophylaxis and as support of clinically significant neutropenia during treatment.

The use of anti-emetics is permitted. Premedications for HMAs are allowed per institutional standard of care.

Routine premedication for infusion reactions should not be administered prior to the first dose of blinded study treatment. However, patients who experience an infusion-related reaction (with the exception of anaphylaxis) may receive subsequent treatment with premedication as described in Section 5.6.1.

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

Hydroxyurea (up to 14 days of therapy) and/or leukapheresis are permitted in the setting of uncontrolled leukocytosis.

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

Concomitant palliative focal external beam radiation may be given for symptomatic control of pain.

### **5.5.3 Prohibited Concomitant Therapy**

Patients may not receive other investigational drugs, immunosuppressive medications (with the exception of the medications listed in Section 5.5.2), non-study systemic anti-neoplastic therapy, or allo-SCT during the treatment period.

If patients become candidates for allo-SCT after enrollment, blinded study treatment must be discontinued at least 30 days prior to initiation of the preparative regimen for allo-SCT.

## **5.6 Management of Adverse Reactions**

### **5.6.1 Management of Infusion Reactions**

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

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

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

### **5.6.2 Overdose**

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

## **5.7 Treatment Compliance**

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

# **6 STUDY ACTIVITIES**

## **6.1 Schedule of Events**

Adverse events and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.7.1.3). Day 1 is the first dose of HMA. Any study protocol-related AE should be recorded from the time of informed consent as well as any concomitant medications given for treatment of the AE. Medical resource utilization (MRU) data will be collected from Day 1 (predose) through EOT.

Separate schedule of events tables are provided for patients treated with azacitidine and those treated with decitabine (see Appendix A). Details of PK, ATA, and biomarker sampling timepoints are provided in Appendix B. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

## **6.2 Screening Visit (Days –28 to 1)**

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history
- Diagnostic bone marrow examination for local baseline disease assessment and cytogenetics (bone marrow aspirate is sufficient; however, if marrow cannot be aspirated, a biopsy may be conducted). A bone marrow assessment performed prior to informed consent and up to 60 days prior to first dose of study treatment may be used.
- Bone marrow sample for central assessment of cytogenetic risk, minimal residual disease (MRD), CD33 expression, profiling for disease-associated somatic mutations or alterations in genes or RNAs commonly altered in hematologic malignancies and other genes or RNAs potentially associated with disease relapse or resistance to vadastuximab talirine
- Serum and plasma sample for central assessment of soluble factors potentially associated with clinical outcome, e.g., sCD33

### **6.2.1 Baseline Visit (Days –7 to Day 1)**

- Physical exam

- Height and weight
- Electrocardiogram (ECG)
- Pulse oximetry testing for oxygen saturation level at room air
- Pregnancy test for females of childbearing potential
- ECOG performance status ([Appendix C](#))
- Collection of data to calculate the Charlson Comorbidity Index (CCI), the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI), and Wheatley Risk group
- Serum chemistry panel
- Complete blood count (CBC) with differential
- EQ-5D
- EORTC-QLQ-C30
- Randomization (to occur within 1 business day of planned first dose of HMA).

### **6.3 Treatment Period (Day 1 to Day 28)**

#### **6.3.1 Day 1 ( $\pm 1$ day) of Each Cycle**

- Physical exam
- Pregnancy test for females of childbearing potential
- Weight
- ECOG performance status ([Appendix C](#))
- Serum chemistry panel
- CBC with differential
- HMA (azacitidine or decitabine) administration
- EQ-5D
- EORTC-QLQ-C30
- Blood sample for ATA (Cycles 1 to 4 and every 4th cycle thereafter)
- Serum and plasma sample for central assessment of soluble factors potentially associated with clinical outcome, e.g., sCD33 (Cycles 1 and 2 only; pre-HMA administration, see [Appendix B](#))

If Baseline Visit activities occur within 1 business day prior to Cycle 1 Day 1, the following assessments do not need to be repeated at the Cycle 1 Day 1 visit: physical exam, ECOG performance status, serum chemistry panel, CBC with differential, and EQ-5D and EORTC-QLQ-C30.

If dosing is delayed due to laboratory abnormalities, CBC with differential and serum chemistry panel should still be sent to the central lab.

#### **6.3.2 Day 2 to 4 of Each Cycle**

- HMA (azacitidine or decitabine) administration

### 6.3.3 Day 5 of Each Cycle

Only for patients receiving azacitidine:

- Azacitidine administration

Only for patients receiving decitabine:

- Physical exam (Cycles 1 and 2 only)
- Serum chemistry panel (Cycles 1 and 2 only)
- CBC with differential (Cycles 1 and 2 only)
- Decitabine administration
- Vital signs (pre- and within 30 minutes post-blinded study treatment administration)
- Blinded study treatment given after decitabine
- Blood sample for PK (predose Cycles 1 and 2 only; postdose all cycles; see [Appendix B](#))
- Serum and plasma sample for central assessment of soluble factors potentially associated with clinical outcome, e.g., sCD33 (Cycles 1 and 2 only; sample taken pre-blinded study treatment administration [see [Appendix B](#)])

### 6.3.4 Day 6 of Each Cycle (only for patients receiving azacitidine; Day 8 if alternative azacitidine dosing schedule used)

- Azacitidine administration

### 6.3.5 Day 7 of Each Cycle (only for patients receiving azacitidine; Day 9 if alternative azacitidine dosing schedule used)

- Physical exam (Cycles 1 and 2 only)
- Serum chemistry panel (Cycles 1 and 2 only)
- CBC with differential (Cycles 1 and 2 only)
- Azacitidine administration
- Vital signs (pre- and within 30 minutes post-blinded study treatment administration)
- Blinded study treatment administration (given after HMA)
- Blood sample for PK (predose Cycles 1 and 2 only; postdose all cycles; see [Appendix B](#))
- Serum and plasma sample for central assessment of soluble factors potentially associated with clinical outcome, e.g., sCD33 (Cycles 1 and 2 only; pre-blinded study treatment administration; see [Appendix B](#))

### 6.3.6 Day 15 ( $\pm 2$ days) of Cycles 1–4 only

- Physical exam
- Serum chemistry panel
- CBC with differential

### **6.3.7 Day 21 ( $\pm 2$ days) of Cycles 1 and 2 only**

- Physical exam
- Serum chemistry panel
- CBC with differential

### **6.3.8 Day 28 ( $-6$ day window) of Each Even Numbered Cycle**

The assessments listed below will be done until CR/CRi. The window may be up to Day 42 in the event of a delay in the start of the next cycle of treatment.

- CBC with differential
- Bone marrow examination for response assessment (bone marrow aspirate is sufficient; however, if marrow cannot be aspirated, a biopsy may be conducted). Cytogenetics are also required if abnormal at baseline.
- Bone marrow sample for central assessment of MRD, CD33 expression, profiling for disease-associated somatic mutations or alterations in genes or RNAs commonly altered in hematologic malignancies and other genes or RNAs potentially associated with disease relapse or resistance to vadastuximab talirine
- Serum and plasma sample for central assessment of soluble factors potentially associated with clinical outcome, e.g., sCD33

After CR/CRi, the above samples and assessments will be conducted according to the following schedule:

- 2 cycles after initial confirmation of CR or CRi
- At the time of conversion from CRi to CR
- At the time of suspected relapse

### **6.4 End of Treatment Visit (30 to 37 days after last dose of study drug)**

End of Treatment (EOT) visits should occur 30 to 37 days after the last dose of any study drug treatment unless delayed due to an AE. However, EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 30 days after the last study treatment, the patient will be contacted 30 to 37 days following the last treatment to assess for adverse events. The following assessments will be done:

- Physical examination
- Pregnancy test for females of childbearing potential
- ECOG performance status ([Appendix C](#))
- Serum chemistry panel
- CBC with differential
- EQ-5D
- EORTC-QLQ-C30
- Blood sample for ATA



The following assessments will also be required if not conducted within 4 weeks of EOT:

- Bone marrow examination for response assessment (bone marrow aspirate is sufficient; however, if marrow cannot be aspirated, a biopsy may be conducted). Cytogenetics are also required if abnormal at baseline.
- Bone marrow sample for central assessment of MRD, CD33 expression, profiling for disease-associated somatic mutations or alterations in genes or RNAs commonly altered in hematologic malignancies or potentially associated with disease relapse or resistance to vadastuximab talirine
- Serum and plasma sample for central assessment of soluble factors potentially associated with clinical outcome, e.g., sCD33

## 6.5 Follow-up

All patients will be contacted every 2 months (or more frequently as needed to support analysis of the study endpoints) after EOT until death or study closure for survival status and collection of subsequent anticancer treatment information.

Events of sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) that occur within 180 days of the last dose of 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 blinded study drug in the absence of relapse and additional therapy will be followed for SOS/VOD for 100 days post-transplant (refer to Section 7.7.1.4).

Patients who discontinue study treatment prior to leukemic relapse or progression will have a CBC with differential done every 2 months through 24 months after EOT, and every 4 months thereafter until initiation of another anticancer treatment, progression or leukemic relapse.

At time of either suspected relapse or conversion from mLFS to CRi/CR or CRi to CR, the following assessments must be done:

- Bone marrow examination for response assessment (bone marrow aspirate is sufficient; however, if marrow cannot be aspirated, a biopsy may be conducted). Cytogenetics are also required if abnormal at baseline.
- Bone marrow sample for central assessment of MRD, CD33 expression, profiling for disease-associated somatic mutations or alterations in genes or RNAs commonly altered in hematologic malignancies and other genes or RNAs potentially associated with disease relapse or resistance to vadastuximab talirine.

## 6.6 End of Study/End of Follow-up

The date the patient met criteria for study discontinuation and the reason for study discontinuation will be recorded.

## 7 STUDY ASSESSMENTS

### 7.1 Screening/Baseline Assessments

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

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

### 7.2 Response/Efficacy Assessments

Treatment response will be assessed locally per investigator by pathology review of bone marrow aspirate/biopsy and flow cytometry analysis of the number of blasts in bone marrow at protocol-specified timepoints (see Section 6 and [Appendix A](#)).

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

Clinical response will be determined at each assessment according to a modification of the response categorization in the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia ([Cheson 2003](#)); see [Appendix E](#). The category of CR with incomplete platelet recovery (CR<sub>p</sub>, also referred to as CR<sub>i</sub>[p]), which has been reported in prior AML trials, will be included as CR<sub>i</sub>.

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

### 7.3 Pharmacokinetic, ATA, and Biomarker Assessments

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

Peripheral blood and bone marrow aspirates will be collected for biomarker studies at the timepoints outlined in [Appendix B](#).

Biomarker assessments may include central assessment of CD33 expression, profiling for disease-associated somatic mutations or alterations in genes or RNAs commonly altered in hematologic malignancies or potentially associated with disease relapse or resistance to

vadastuximab talirine. Additional assessments may include measurement of soluble factors potentially associated with clinical outcome, e.g., sCD33.

MRD will be assessed by a central laboratory in bone marrow samples (see the Research Specimen Manual for details).

#### **7.4 Biospecimen Repository**

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

#### **7.5 Patient Reported Outcome Assessments**

Two validated tools will be used: the EORTC Quality of Life Questionnaire, QLQ-C30, and the EuroQol 5-dimensions (EQ-5D).

PRO assessments should be completed before any other procedures at the study visits noted in the schedule of events ([Appendix A](#)).

##### **7.5.1 EORTC Core Quality of Life Questionnaire, QLQ-C30**

The EORTC Quality of Life Questionnaire was developed to measure aspects of quality of life pertinent to patients with a broad range of cancers who are participating in clinical trials ([Aronson 1993](#); [Sneeuw 1998](#)). The current version of the core instrument (QLQ-C30, version 3) is a 30-item questionnaire consisting of the following:

- 5 functional domains (physical, role, cognitive, emotional, social);
- 3 symptom scales (fatigue, pain, nausea & vomiting);
- Single items for symptoms (shortness of breath, loss of appetite, sleep disturbance, constipation, diarrhea) and financial impact of the disease; and
- 2 global items (health, overall quality of life).

##### **7.5.2 EuroQol-5 Dimensions**

The EQ-5D is a standardized instrument developed by the EuroQol Group for use as a generic, preference-based measure of health outcome. It is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status. The EQ-5D is a 5-item self-reported measure of functioning and well-being, which assesses 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension comprises 3 levels (no problems, some/moderate problems, extreme problems). A unique EQ-5D health state is defined by combining 1 level from each of the 5 dimensions. This questionnaire also records the

respondent's self-rated health status on a vertical graduated (0 to 100) visual analogue scale. Responses to the 5 items will also be converted to a weighted health state index (utility score) based on values derived from general population samples. The EQ-5D is recommended for use in cost-effectiveness analyses commonly employed in health technology assessments by the Washington Panel on Cost Effectiveness in Health and Medicine ([Gold 1996](#)).

## **7.6 Medical Resource Utilization**

During the study, all medical care encounters that occur from Day 1 (predose) through EOT will be collected for all patients. MRU data will not be collected for per-protocol study visits and procedures. Examples of data to be collected are transfusion requirements, number of medical care encounters, such as hospital admissions, outpatient and home visits, and emergency room visits, and major diagnostic procedures.

## **7.7 Safety Assessments**

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

Safety will be monitored over the course of the study by an IDMC as described in [Section 9.3.10](#).

### **7.7.1 Adverse Events**

#### **7.7.1.1 Definitions**

##### **Adverse Event**

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

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

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing 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 post-dose) through the end of the safety reporting period (see

Section 7.7.1.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.

- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a serious adverse event (SAE), or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record “anemia” rather than “low hemoglobin”).

### **Serious Adverse Events**

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

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

### **Adverse Event Severity**

AE severity should be graded using the National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. These criteria are provided in the study manual.

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

## Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment 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: <ul style="list-style-type: none"><li>• an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)</li><li>• an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)</li></ul>
Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

### 7.7.1.2 Procedures for Eliciting and Recording Adverse Events

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

#### Eliciting Adverse Events

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

#### Recording Adverse Events

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

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

#### Diagnosis vs. Signs or Symptoms

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

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For infusion-related reactions, do not use the NCI CTCAE terms of 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or hypersensitivity reaction.'

Instead, record each sign or symptom as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

### **Recording Serious Adverse Events**

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

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

### **Progression of the Underlying Cancer**

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

### **Pregnancy**

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

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

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the ‘serious’ criterion above (see definitions Section 7.7.1.1) should be reported as SAEs.

### **7.7.1.3 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 the EOT visit or 30 days after the last study treatment, whichever is later. However, all study protocol-related AEs are to be recorded from the time of informed consent. All SAEs that occur after the safety reporting period and are considered study 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 patient dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

### **7.7.1.4 Adverse Events of Special Interest**

Hepatobiliary serious adverse events, including cases of sinusoidal obstruction syndrome/veno-occlusive disease (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 blinded study treatment will be reported to the sponsor. Patients who undergo subsequent allo-SCT in the absence of relapse and additional therapy will be followed for SOS/VOD to 100 days post-transplant.

### **7.7.1.5 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:

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

The completed SAE form and SAE Fax Cover Sheet are to be emailed or faxed to the sponsor’s Drug Safety Department at **1 (425) 527-4308** or [Drug.Safety@Seagen.com](mailto:Drug.Safety@Seagen.com) within 24 hours.

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



### **7.7.1.6 Sponsor Safety Reporting to Regulatory Authorities**

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section [7.7.1.5](#)).

The sponsor will report all SAEs to regulatory authorities as required per local regulatory reporting requirements. In the United States, endpoints that assess disease-related mortality or major morbidity as well other SAEs that are not study endpoints, but are known consequences of the underlying disease or condition that are anticipated to occur in the study population should not be reported to the Food and Drug Administration (FDA) as individual IND safety reports per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's guidance Safety Reporting Requirements for INDs and BA/BE Studies (December 2012) and FDA's guidance Safety Assessment for IND Safety Reporting (December 2015).

In this study, the SAEs that do not require individual IND safety reports to the FDA are leukemic relapse. Events of febrile neutropenia are anticipated in this population and individual IND safety reports will not be submitted to FDA. However, the sponsor will report all SAEs, including anticipated events, to international authorities as required per local reporting requirements.

All SAEs will be reviewed periodically by an IDMC.

### **7.7.2 Clinical Laboratory Tests**

Samples will be drawn for central and local labs. Local laboratory testing will include institutional standard tests for evaluating safety and making clinical decisions.

The following laboratory assessments will be performed by the central laboratory to evaluate safety at scheduled timepoints (see [Appendix A](#)) during the course of the study:

- The chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, lipase, magnesium, amylase, and uric acid.
- The CBC with differential is to include the following tests: white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, blasts, RBC count, mean corpuscular volume (MCV), hemoglobin and hematocrit.

### **7.7.3 Physical Examination**

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

#### **7.7.4 Cardiac Monitoring**

ECGs will be conducted at baseline. Paper copies of the tracings will be used for data entry into the CRF. Additional ECGs should be conducted if clinically indicated.

#### **7.7.5 ECOG Performance Status**

ECOG performance status ([Appendix C](#)) will be evaluated at protocol-specified time points.

#### **7.7.6 Vital Signs**

Vital signs: temperature, heart rate, respiratory rate, and blood pressure, will be evaluated at protocol-specified time points.

### **7.8 Appropriateness of Measurements**

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications. Adverse events and, when applicable, clinical laboratory data will be graded using NCI CTCAE, Version 4.03.

Clinical response will be determined according to a modification of the response categorization in the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia ([Cheson 2003](#)) (see [Appendix E](#)). These criteria are considered standard in oncological practice, and the intervals of evaluation in this protocol are appropriate for disease management.

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

Molecular characterization of disease is common in oncological practice. Biomarker samples will be collected at intervals coincident with pharmacokinetic sampling or clinical assessments appropriate for disease management.

## **8 DATA QUALITY CONTROL AND QUALITY ASSURANCE**

### **8.1 Site Training and Monitoring Procedures**

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of patients at the site, Seattle Genetics or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current Investigator's Brochure/ package insert
- Recording and reporting AE and SAE

- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval process
- Informed consent process
- Good Clinical Practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing and record keeping
- Patient coding and randomization (if applicable)
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

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

## **8.2 Data Management Procedures**

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

## **8.3 Access to Source Data**

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect patient confidentiality are to be employed

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

#### **8.4 Accuracy and Reliability of Data**

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

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

#### **8.5 Quality Assurance Procedures**

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

#### **8.6 Data Handling and Record Keeping**

##### **8.6.1 Data Handling**

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

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

##### **8.6.2 Investigator Record Retention**

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and Institution in which the study will be conducted, or for the period specified by Seattle Genetics, whichever is longer. The investigator must contact Seattle Genetics prior to destroying any records associated with the

study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Seattle Genetics.

## **9 DATA ANALYSIS METHODS**

### **9.1 Determination of Sample Size**

There are 2 primary endpoints for this study: CRc rate and OS. To maintain strong control of the type I error rate at 0.05, a fallback procedure proposed by Wiens will be used in the testing of the primary endpoints, with an alpha of 0.01 pre-assigned to CRc rate and an alpha of 0.04 pre-assigned to OS (Wiens 2005).

The sample size was calculated based on maintaining 90% power to test both primary endpoints and to account for 2 planned interim analyses for OS, one futility analysis at 30% and one interim efficacy analysis at 60% of the targeted number of OS events, using the O'Brien-Fleming method.

For the primary endpoint of CRc rate, at least 308 patients are required to provide 90% power to detect an improvement in CRc rate from 20% to 40% using a chi-squared test at a significance level of 0.01.

For the primary endpoint of OS, approximately 354 OS events are required with 90% power to detect a hazard ratio of 0.70 (12.9 months median OS in the experimental arm [vadastuximab talirine plus HMA] versus 9 months for the comparator arm [placebo plus HMA]) using a 2-sided log-rank test at an alpha of 0.04.

To provide adequate power for both primary endpoints, a total of 540 patients will be randomized in a 1:1 ratio to either the experimental arm or the comparator arm, assuming an accrual period of 26 months with a slower rate of accrual for the first 6 months, a 12-month follow up, and a 5% yearly drop-out rate.

EAST (Version 6.3) was used to calculate and validate the sample size.

### **9.2 Study Endpoint Definitions**

#### **9.2.1 Primary Endpoints**

##### **9.2.1.1 Composite Complete Remission (CRc) Rate**

CRc rate is defined as the proportion of patients who achieve CR or CRi according to the modified response criteria for AML (Cheson 2003) defined in Appendix E. Patients whose disease response cannot be assessed will be considered non-responders for calculating the CRc rate.

### **9.2.1.2 Overall Survival (OS)**

Overall survival (OS) is defined as the time from randomization to death due to any cause. Specifically,

$$\text{OS} = \text{Date of death} - \text{Date of randomization} + 1.$$

For a patient who is not known to have died by the end of study follow up, observation of OS is censored on the date the patient was last known to be alive (i.e., date of last contact). Patients lacking data beyond the day of randomization will have their survival time censored on the date of randomization (i.e., OS duration of 1 day).

## **9.2.2 Secondary Efficacy Endpoints**

### **9.2.2.1 MRD-negative CRc Rate**

MRD-negative CRc rate is defined as the proportion of patients who achieve both morphologic remission (CR or CRi) and MRD-negative status. Patients whose morphologic response or MRD status cannot be assessed will be considered non-responders for calculating the MRD-negative CRc rate.

### **9.2.2.2 Duration of Remission**

Duration of remission is defined as the time from the first documentation of CR or CRi to the first documentation of disease relapse or to death due to any cause, whichever comes first. Patients who have started a new antitumor therapy (excluding maintenance therapy during remission in the absence of relapse, or consolidative allogeneic or autologous stem cell transplant after study treatment) prior to documentation of disease relapse will be censored at the date of the last response assessment on or prior to start of new therapy.

Duration of remission will be calculated only for the subgroup of patients achieving a CR or CRi.

### **9.2.2.3 Event-Free Survival (EFS)**

EFS is defined as the time from randomization to the first documentation of progression, disease relapse (see [Appendix E](#)) or to death due to any cause, whichever comes first. Patients who have started an antitumor therapy (excluding maintenance therapy during remission in the absence of relapse, or consolidative allogeneic or autologous stem cell transplant after study treatment) other than the study treatment prior to documentation of progression or disease relapse will be censored at the date of the last response assessment on or prior to start of new therapy.

### **9.2.2.4 Leukemia-Free Survival (LFS)**

LFS is defined as the time from the first documentation of blast clearance (morphologic leukemia-free state [mLFS], CR or CRi) to the first documentation of disease relapse or to death due to any cause, whichever comes first (see [Appendix E](#)). Patients who have started an antitumor therapy (excluding maintenance therapy during remission in the absence of

relapse, or consolidative allogeneic or autologous stem cell transplant after study treatment) other than the study treatment prior to documentation of progression or disease relapse will be censored at the date of the last response assessment on or prior to start of new therapy.

LFS will be calculated only for the subgroup of patients achieving a CR or CRi.

#### **9.2.2.5 Time to Complete Remission**

Time to complete remission (TTCR) is defined as the time from randomization to the first documentation of CR or CRi. TTCR will be calculated only for the subgroup of patients achieving a CR or CRi.

#### **9.2.2.6 Mortality Rates**

The 30-day mortality rate is defined as the proportion of patients who die within 30 days of randomization. The 60-day mortality rate is defined as the proportion of patients who die within 60 days of randomization.

### **9.3 Statistical and Analytical Plans**

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

#### **9.3.1 General Considerations**

##### **9.3.1.1 Randomization and Blinding**

This is a randomized study that will enroll approximately 540 patients. Patients will be randomized in a 1:1 manner to receive either vadastuximab talirine plus HMA or placebo plus HMA.

Patients will be stratified based on the following variables to ensure that patient-specific risk factors are appropriately balanced between treatment arms:

- Cytogenetic risk per revised UK MRC classification (intermediate versus adverse; see [Appendix D](#))
- ECOG performance status (0–1 versus 2)
- HMA (azacitidine versus decitabine)
- Age (<75 years versus ≥75 years)

After stratification, patients will be randomized into 1 of 2 treatment arms, for a total of approximately 270 patients per arm.

Randomization will be performed centrally using a system that will assign a unique patient randomization number. The actual treatment assignment will remain blinded. Randomization procedures are detailed in the Study Manual.

### **9.3.1.2 Adjustments for Covariates**

Stratified analyses will include adjustment for the stratification factor as recorded at randomization (described in Section 9.3.1.1). Other covariates may be considered for adjustment in exploratory analyses.

### **9.3.1.3 Handling of Dropouts and Missing Data**

Missing data will not be imputed, with the exception of AE dates while calculating duration of events and treatment-emergent status. Patients with missing values of a variable other than response endpoints (CRc rate, MRD-negative CRc rate) and time-to-event endpoints (OS, LFS, and EFS) will be excluded from the analysis of that endpoint. Patients whose disease response cannot be assessed will be scored as non-responders for calculating the CRc rate and MRD-negative CRc rate. Censoring rules will be applied to the estimation of the distribution of the time-to-event endpoints, details will be provided in the SAP.

### **9.3.1.4 Multicenter Studies**

There are multiple centers in this study, however it is not anticipated that any center will accrue enough patients to warrant an analysis by center.

### **9.3.1.5 Multiple Comparisons and Multiplicity**

To maintain strong control of the Type I error rate at 0.05, the fallback procedure proposed by Wiens will be used in the testing of the primary endpoints, with an alpha of 0.01 pre-assigned to CRc rate and an alpha of 0.04 pre-assigned to OS. (Wiens 2005). If the test for the CRc rate is statistically significant, then the alpha of 0.01 will be re-allocated to OS, and the test for OS will be performed at a 2-sided alpha of 0.05. If the test for the CRc rate is not statistically significant, then the test for OS will be performed at a 2-sided alpha of 0.04.

The parallel gatekeeping principle will be used to control the overall type I error rate of 0.05 (Dmitrienko 2011). The primary endpoints, CRc rate and OS (family 1), will be the gatekeepers for testing the secondary endpoint of MRD-negative CRc rate (family 2). If at least one of the primary endpoints is statistically significant, then a statistical test will be performed for the MRD-negative CRc rate. If both CRc rate and OS are statistically significant, then MRD-negative CRc rate will be tested at an overall alpha of 0.05. If only one of the 2 primary endpoints is statistically significant, then MRD-negative CRc rate will be tested at the corresponding alpha level of the significant primary endpoint. If the tests for both CRc rate and OS are not statistically significant, then the p-value of the test for MRD-negative CRc rate will still be calculated but will be considered descriptive.

Two formal interim analyses for OS are planned. The test significance level for OS at the interim analysis will be adjusted based on the actual number of OS events observed at each interim analysis according to the O'Brien-Fleming spending function.



### **9.3.1.6 Data Transformations and Derivations**

For efficacy assessments, the date of response will be the latest of all applicable dates for the given assessment (e.g., bone marrow date, CBC date). The date of relapse/progression will be the earliest of all applicable dates for the given assessment. Detailed methodology will be provided in the SAP.

### **9.3.1.7 Analysis Sets**

The intent-to-treat (ITT) analysis set will include all randomized patients. Patients will be included in the treatment group assigned at randomization regardless of any actual treatment received.

The modified intent-to-treat (mITT) analysis set will include all patients from the ITT analysis set who receive any dose of blinded study treatment (vadastuximab talirine or placebo) or HMA. Patients will be included in the treatment group assigned at randomization regardless of the actual treatment received.

The safety analysis set will include all patients who receive any dose of blinded study treatment (vadastuximab talirine or placebo) or HMA. Treatment group will be determined using the actual treatment received, regardless of the randomization treatment assignment. Patients receiving any dose of vadastuximab talirine will be grouped into the experimental arm. Patients who do not receive vadastuximab talirine but receive any dose of HMA will be grouped into the comparator arm.

### **9.3.1.8 Examination of Subgroups**

As exploratory analyses, subgroup analyses may be conducted for selected endpoints, including, but not limited to gender, race, AML subtype, and randomization strata (cytogenetic risk, ECOG performance status, HMA, and age). Detailed methodology will be provided in the SAP.

### **9.3.1.9 Timing of Analyses**

The primary analysis of CRc rate is planned when the following 2 conditions are met: 1) 6 months after 308 patients have been randomized, and 2) approximately 212 OS events have occurred. The estimated duration of the study through the primary analysis of CRc rate is approximately 2 years from randomization of the first patient based on design assumptions. Only the first 308 patients randomized will be included in the primary analysis of CRc rate. CRc rate will also be analyzed for all randomized patients at the time of the final analysis.

The estimated duration of the study through the final analysis for OS is approximately 3 years from randomization of the first patient based on design assumptions.

There are 2 planned interim analyses of OS. The first interim analysis will take place when approximately 106 OS events have occurred (~30% of the targeted number of events) and will assess the futility of vadastuximab talirine in combination with azacitidine or decitabine.

The second interim analysis for OS will occur in conjunction with the primary analysis of CRc rate. The analysis will be conducted when the following 2 conditions are met: 1) 6 months after 308 patients have been randomized, and 2) approximately 212 OS events have occurred (~60% of the targeted number of events). The interim OS results will be assessed for early stopping for efficacy.

The IDMC will provide recommendations to the sponsor's Data Review Board as to appropriate study direction at the interim analysis.

End-of-trial is defined as the point at which all patients have died or discontinued the study, or have been followed for a maximum of 3 years after the last patient enrolled, whichever comes first. An end-of-trial analysis will be performed after study closure.

### **9.3.2 Patient Disposition**

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

### **9.3.3 Patient Characteristics**

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

### **9.3.4 Treatment Compliance**

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

### **9.3.5 Efficacy Analyses**

All efficacy endpoints will be analyzed using the ITT analysis set. Supplemental analyses will be performed using the mITT analysis set.

#### **9.3.5.1 Primary Efficacy Analysis**

**CRc rate** will be analyzed based on the ITT analysis set. The CRc rate between the 2 treatment arms will be compared using a Cochran-Mantel-Haenszel test stratified by the randomization strata. The CRc rate and its 2-sided 99% confidence interval (CI) will be summarized by treatment arm. At the time of the primary analysis of CRc rate, only the first 308 patients randomized will be included in the population for the analysis of CRc rate. CRc rate will also be analyzed for all randomized patients at the time of the final analysis.

**Overall survival** will be assessed using Kaplan-Meier methods. A stratified log-rank test without adjustments for covariates will be used in the primary evaluation of OS differences between the 2 treatment arms based on the ITT population. The hazard ratio will be estimated using the unadjusted stratified Cox model. The 2-sided 95% CI and the CI corresponds to the significance level of the test following the multiplicity adjustment (see Section [9.3.1.5](#)) will be presented. The proportional hazard assumptions will be examined and sensitivity analyses

will be conducted if appropriate. All events entered in the database at the time of the analysis and source-data verified will be included in the analysis of OS, even if there is more than the pre-specified number of events.

Kaplan-Meier curves depicting OS in the 2 treatment arms will be generated. Additionally, the median OS and the probability of OS from 1 month to the end of the follow-up period will be reported at pre-specified intervals. The associated 2-sided 95% CIs will be calculated using the complementary log-log transformation method (Collett 1994). Detailed methodology will be provided in the SAP.

### 9.3.5.2 Secondary Efficacy Analyses

**MRD-negative CRc rate:** MRD-negative CRc rate will be analyzed based on the ITT analysis set. The MRD-negative CRc rate between the 2 treatment arms will be compared using a Cochran-Mantel-Haenszel test stratified by the randomization strata. The MRD-negative CRc rate and its 2-sided 95% CI will be summarized by treatment arm.

**Duration of remission:** Duration of remission will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided by treatment arm using the ITT analysis set. The median remission duration and its 2-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated by treatment arm.

**Event-free survival:** EFS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided by treatment arm using the ITT analysis set. The median EFS and its 2-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated by treatment arm.

**Leukemia-free survival:** LFS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided by treatment arm using the ITT analysis set. The median LFS and its 2-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated by treatment arm.

**Time to complete remission:** TTCR will be summarized by treatment arm using descriptive statistics.

### 9.3.6 Pharmacokinetic, ATA, and Biomarker Analyses

Observed plasma vadastuximab talirine ADC and SGD-1882 (if measurable) will be summarized with descriptive statistics at each PK sampling timepoint. These data may be combined with data from previous studies for population PK and PK/PD analyses. The relationship between vadastuximab talirine PK and PD endpoints, safety, or efficacy may be explored; these analyses, if conducted, will be descriptive.

The incidence of ATA will be summarized by descriptive statistics.

Biomarker assessments will also be summarized using descriptive statistics.

### **9.3.7 Patient Reported Outcomes Analyses**

PRO analyses will be conducted using the ITT analysis set and will assess the change from baseline to the end of treatment in PRO assessments. QLQ-C30 scores will be determined per patient self-report. Change from baseline to end of treatment in QLQ-C30 scores will be summarized using descriptive statistics.

EQ-5D Health Index Scores will be determined by patient self-report. The EQ-5D health state index and visual analog scale will be summarized descriptively by visit.

### **9.3.8 MRU Analyses**

MRU data will be summarized using descriptive statistics. Details will be provided in the SAP.

### **9.3.9 Safety Analyses**

All safety analyses will be performed using the safety analysis set unless otherwise specified.

#### **9.3.9.1 Extent of Exposure**

Duration of treatment, number of cycles, total dose and dose intensity may be summarized by treatment agent and arm. Dose modifications will also be summarized. Details will be provided in the SAP.

#### **9.3.9.2 Adverse Events**

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

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

#### **9.3.9.3 Deaths and Serious Adverse Events**

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

#### **9.3.9.4 Clinical Laboratory Results**

Summary statistics for actual values and for change from baseline may be tabulated as appropriate for selected laboratory results by treatment arm and scheduled visit. Patients with laboratory values outside of the normal reference range at any postbaseline assessment will be listed.

### **9.3.9.5 Other Safety Analyses**

#### **ECOG Status**

ECOG status may be summarized for each visit. Shifts from baseline to the best and worst postbaseline score may be tabulated.

#### **Vital Signs**

Vital signs will be summarized. Changes in vital sign measurements from pre-dose to post-dose of blinded study treatment may be tabulated.

#### **Hospitalizations**

Hospitalization data will be summarized. Details will be provided in the SAP.

#### **Transfusions**

RBC and platelet transfusion independence will be summarized. Details will be provided in the SAP.

### **9.3.10 Interim Analyses**

An IDMC will periodically monitor the trial for safety, including SAEs and early mortality, during the treatment period. During the periodical safety review, the IDMC will evaluate the 60-day mortality rates in the 2 treatment arms. The independent statistician will assist the IDMC to evaluate whether there is an increased risk of early death in the experimental arm and make appropriate recommendations to the sponsor.

Two formal interim analyses for OS are planned for the study. The first interim analysis is for the purpose of futility testing and will be conducted when approximately 106 OS events have occurred (~30% of the targeted number of events). The second interim analysis is for superiority testing and will occur in conjunction with the primary analysis of CRc rate. The analysis will be conducted when the following 2 conditions are met: 1) 6 months after 308 patients have been randomized, and 2) approximately 212 OS events have occurred (~60% of the targeted number of events). The stopping boundaries will be determined using Lan-DeMets spending functions to simulate O'Brien-Fleming boundaries. Details will be provided in the SAP.

The IDMC will provide recommendations to the sponsor's Data Review Board as to appropriate study direction. The sponsor will remain blinded to treatment assignment. See the IDMC Charter for details.

## **10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS**

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 (Brazil 2013), and all applicable regulatory requirements.

### **10.1 Informed Consent**

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

### **10.2 Ethical Review**

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

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

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

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

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

### **10.3 Regulatory Considerations**

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

#### **10.3.1 Investigator Information**

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

### **10.3.2 Protocol Amendments and Study Termination**

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

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

### **10.4 Study Documentation, Privacy and Records Retention**

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

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

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

### **10.5 Clinical Trial Agreement**

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

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## APPENDIX A-1: SCHEDULE OF EVENTS – AZACITIDINE

	Visit Window	Screening Within 28D prior to first dose of HMA	Baseline Within 7D prior to first dose of HMA	Enrollment Within 7D prior to first dose of HMA	Each Cycle						EOT <sup>G</sup> 30–37 days post last dose of HMA/blinded study treatment	LTFU ±2 wks		
					D1 ±1D	D2–5	D6 <sup>O</sup>	D7 <sup>M</sup>	D15 ±2D	D21 ±2D			D28	
Baseline and Safety Assessments	Informed consent	X		Eligibility documentation submitted to sponsor prior to study start										
	Inclusion/exclusion	X												
	Medical history	X												
	Diagnostic bone marrow exam, including cytogenetics	X <sup>W</sup>												
	Physical examination		X			X <sup>P</sup>			X <sup>O</sup>	X <sup>D</sup>	X <sup>O</sup>		X	
	Vital signs								X <sup>Y</sup>					
	Weight		X <sup>C</sup>			X								
	ECG		X											
	Pulse oximetry for oxygen saturation		X											
	Pregnancy test (females of childbearing potential)		X			X							X	
	ECOG performance status		X			X <sup>P</sup>							X	
	Collect data to calculate CCI and HCT-CI and Wheatley Risk		X											
	Serum chemistry		X			X <sup>P,U</sup>			X <sup>O</sup>	X <sup>D</sup>	X <sup>O</sup>		X	
	CBC with differential		X			X <sup>P,U</sup>			X <sup>O</sup>	X <sup>D</sup>	X <sup>O</sup>	X <sup>K,S</sup>	X	X <sup>J</sup>
Randomization				X <sup>N</sup>										
Con meds & AEs		Collect any related to study protocol procedures			Collect pre-Day 1 HMA dose through 30 days post last dose of study treatment or EOT visit, whichever is later						X <sup>X</sup>			
Treatment Administration	Blinded study treatment <sup>E</sup>							X						
	Azacitidine <sup>E</sup>				X	X	X	X						
QoL/MRU	EQ-5D and QLQ-C30		X		X <sup>P</sup>							X		
	Medical resource utilization				Collect from Day 1 to EOT									
PK/ATA	Blood sample for PK							X <sup>F</sup>						
	Blood sample for ATA				X <sup>R</sup>							X		
Biomarkers	Bone marrow for cytogenetic risk assessment <sup>A</sup>	X												
	Bone marrow for MRD, CD33 expression & RNA/DNA <sup>A</sup>	X								X <sup>K,S</sup>	X <sup>H</sup>	X <sup>S,V</sup>		
	Serum and plasma sample for soluble factors <sup>A</sup>	X			X <sup>L,O</sup>		X <sup>L,O</sup>			X <sup>K,S</sup>	X <sup>H</sup>			
Response Assessments	Bone marrow examination <sup>B</sup>									X <sup>K,S,T</sup>	X <sup>H,T</sup>	X <sup>S,T,V</sup>		
	Survival status												X <sup>I</sup>	

A By central assessment.

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

C Include assessment of height.

D Cycles 1–4 only.

E Alternative schedule of treatment administration permitted: azacitidine daily x 5/2 days off/2 days on and vadastuximab talirine or placebo given on Day 9.

F Relative to blinded study drug administration: Cycles 1 and 2, sample obtained predose (within 8 hr prior); all cycles, samples obtained within 15 minutes post administration.

G EOT evaluations should be obtained before initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following last study treatment, conduct a phone screen 30–37 days after the patient's last study treatment to ensure that no changes in AE profile have occurred.

H Only required if not conducted within 4 weeks prior to EOT.

I Contact patient for survival status and collection of subsequent anticancer treatment information every 2 mos (or more frequently as needed to support analysis of the study endpoints) after EOT until death or study closure.

J If study treatment discontinued prior to leukemic relapse or progression, obtain every 2 mos through 24 mos after EOT, and every 4 mos thereafter, until initiation of another anticancer treatment, progression, or leukemic recurrence.

K Day 22–28 in even-numbered cycles until CR/CRi. Window may be up to Day 42 in the event of a delay in the start of the next cycle of treatment. Additional bone marrow examinations should be performed and submitted as clinically indicated to confirm cellular recovery.

L Sample obtained pre-dose HMA on Day 1 and pre-dose blinded study drug on Day 7.

M Day 8 if alternative azacitidine schedule used.

N Randomization to occur after eligibility determined and within 1 business day of planned 1st HMA dose.

O Cycles 1 and 2 only.

P Does not need to be repeated if done within 1 business day of Cycle 1 Day 1.

Q Day 8 if alternative azacitidine schedule used.

R Required in Cycle 1–4 and every fourth cycle thereafter.

S Required 2 mos after confirmation of CR/CRi & at time of conversion from CRi to CR and/or time of suspected relapse.

T If cytogenetics are abnormal at baseline, they are required post-treatment.

U If dosing is delayed due to lab abnormalities, CBC with differential & serum chemistry should still be sent to the central lab.

V If patient is not in CR/CRi, should be done every 2 mos through 24 mos after EOT, and then every 4 mos until CR/CRi.

W Can be done up to 60 days prior to first dose of study treatment

X See Sections 6.5 and 7.7 1.4 for details of follow up for adverse events of special interest

Y Pre- and within 30 minutes post-blinded study treatment administration

## APPENDIX A-2: SCHEDULE OF EVENTS – DECITABINE

	Visit Window	Screening	Baseline	Enrollment	Each Cycle						EOT <sup>F</sup> 30–37 days post last dose of HMA/blinded study treatment	LTFU ±2 wks		
		Within 28D prior to first dose of HMA	Within 7D prior to first dose of HMA	Within 7D prior to first dose of HMA	D1	D2–4	D5	D15	D21	D28				
Baseline and Safety Assessments	Informed consent	X		Eligibility documentation submitted to sponsor prior to study start										
	Inclusion/exclusion	X												
	Medical history	X												
	Diagnostic bone marrow exam, including cytogenetics	X <sup>T</sup>												
	Physical examination		X			X <sup>N</sup>		X <sup>M</sup>	X <sup>D</sup>	X <sup>M</sup>			X	
	Vital signs							X <sup>V</sup>						
	Weight		X <sup>C</sup>			X								
	ECG		X											
	Pulse oximetry for oxygen saturation		X											
	Pregnancy test (females of childbearing potential)		X			X							X	
	ECOG performance status		X			X <sup>N</sup>							X	
	Collect data to calculate CCI, HCT-CI, and Wheatley Risk		X											
	Serum chemistry		X			X <sup>N,R</sup>		X <sup>M</sup>	X <sup>D</sup>	X <sup>M</sup>			X	
	CBC with differential		X			X <sup>N,R</sup>		X <sup>M</sup>	X <sup>D</sup>	X <sup>M</sup>	X <sup>J,P</sup>		X	X <sup>I</sup>
	Randomization					X <sup>L</sup>								
Con meds & AEs		Collect any related to study protocol procedures			Collect pre-Day 1 HMA dose through 30 days post last dose of study treatment or EOT visit, whichever is later						X <sup>U</sup>			
Treatment Administration	Blinded study treatment						X							
	Decitabine				X	X	X							
QoL/MRU	EQ-5D and QLQ-C30		X		X <sup>N</sup>						X			
	Medical resource utilization				Collect from Day 1 to EOT									
PK/ATA	Blood sample for PK						X <sup>E</sup>							
	Blood sample for ATA				X <sup>O</sup>						X			
Biomarkers	Bone marrow for cytogenetic risk assessment <sup>A</sup>	X												
	Bone marrow for MRD, CD33 expression & RNA/DNA <sup>A</sup>	X							X <sup>J,P</sup>		X <sup>G</sup>	X <sup>P,S</sup>		
	Serum and plasma sample for soluble factors <sup>A</sup>	X			X <sup>K,M</sup>		X <sup>K,M</sup>		X <sup>J,P</sup>		X <sup>G</sup>			
Response Assessments	Bone marrow examination <sup>B</sup>								X <sup>J,P,Q</sup>		X <sup>G,Q</sup>	X <sup>P,Q,S</sup>		
	Survival status											X <sup>H</sup>		

A By central assessment.

B Bone marrow aspirate is sufficient; however, if marrow cannot be aspirated, a biopsy may be conducted.

C Include assessment of height.

D Cycles 1–4 only.

E Relative to blinded study drug administration: Cycles 1 and 2, sample obtained predose (within 8 hr prior); all cycles, samples obtained within 15 minutes post administration.

F EOT evaluations should be obtained before initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following last study treatment, conduct a phone screen 30–37 days after the patient's last study treatment to ensure that no changes in AE profile have occurred.

G Only required if not conducted within 4 weeks prior to EOT.

H Contact patient for survival status and collection of subsequent anticancer treatment information every 2 mos after EOT (or more frequently as needed to support analysis of the study endpoints) until death or study closure.

I If study treatment discontinued prior to leukemic relapse or progression, obtain every 2 mos through 24 mos after EOT, and every 4 mos thereafter, until initiation of another anticancer treatment, progression, or leukemic recurrence.

J Day 22–28 in even-numbered cycles until CR/CRi. Window may be up to Day 42 in the event of a delay in the start of the next cycle of treatment. Additional bone marrow examinations should be performed and submitted as clinically indicated to confirm cellular recovery.

K Sample obtained pre-dose HMA on Day 1 and pre-dose blinded study drug on Day 5.

L Randomization to occur after eligibility determined and within 1 business day of planned 1st HMA dose.

M Cycles 1 and 2 only.

N Does not need to be repeated if done within 1 business day of Cycle 1 Day 1

O Required in Cycle 1–4 and every fourth cycle thereafter.

P Required 2 mos after confirmation of CR/CRi & at time of conversion from CRi to CR or time of suspected relapse.

Q If cytogenetics are abnormal at baseline, they are required post-treatment.

R If dosing is delayed due to lab abnormalities, CBC with differential and serum chemistry should still be sent to the central lab.

S If patient is not in CR/CRi, should be done every 2 mos through 24 mos after EOT, and then every 4 mos until CR/CRi.

T Can be done up to 60 days prior to first dose of study treatment

U See Sections 6.5 and 7.7.1.4 for details of follow-up for adverse events of special interest

V Pre- and within 30 minutes post-blinded study treatment administration

## APPENDIX B: PHARMACOKINETIC, ATA, AND BIOMARKER SAMPLING TIMEPOINTS

Cycle	Study Day	Timing	Window	Blood			Bone Marrow Aspirate		
				PK	ATA	Serum and Plasma Samples for Soluble Factors	Cytogenetic Risk Assessment	MRD and CD33 Expression	RNA/DNA for Molecular Profiling
Baseline/ Screening		Within 28D prior to first HMA dose				X	X	X	X
All cycles	D1	Pre-HMA dose	Within 24h		X <sup>A</sup>	X <sup>B</sup>			
	D5 or 7 <sup>C</sup>	Pre-blinded study treatment dose	Within 8h	X <sup>B</sup>		X <sup>B</sup>			
		Post-blinded study treatment dose	Within 15 min	X					
	D28		D22–28			X <sup>D</sup>		X <sup>D</sup>	X <sup>D</sup>
EOT	D30–37	Before initiation of non-protocol therapy			X	X <sup>E</sup>		X <sup>E</sup>	X <sup>E</sup>
Long-term follow-up								X <sup>F</sup>	X <sup>F</sup>

A Required in Cycle 1–4 and every fourth cycle thereafter.

B Cycles 1 and 2 only; sample obtained predose.

C Day 5 for decitabine; Day 7 for azacitidine (or Day 9 if alternative azacitidine dosing schedule used).

D Day 22–28 in even-numbered cycles until CR/CRi. Window may be up to Day 42 in the event of a delay in the start of treatment. After CR/CRi, assessed according to the following schedule: 2 cycles after initial confirmation of CR or CRi, at the time of conversion from CRi to CR, and at the time of suspected relapse.

E Only required if not conducted within 4 weeks prior to EOT.

F Only required 2 months after confirmation of CR/CRi and at the time of conversion from CRi to CR or suspected relapse.

## APPENDIX C: ECOG AND KARNOFSKY PERFORMANCE STATUS

### ECOG

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

### KARNOFSKY

Score	Description
100	Normal; no evidence of disease
90	Minor signs or symptoms
80	Normal activity with effort; some signs or symptoms
70	Cares for self; unable to carry on normal activity
60	Occasional assistance required; capable of most self-care
50	Requires assistance, frequent medical care
40	Disabled; requires special care/assistance
30	Severely disabled; hospitalization indicated
20	Hospitalization necessary; requires active supportive care
10	Moribund; progressing rapidly
0	Dead

**APPENDIX D: REVISED MRC PROGNOSTIC CLASSIFICATION BASED ON  
MULTIVARIABLE ANALYSES**

Cytogenetic Abnormality
<p><b>Favorable – (Not eligible; Exclusion criterion 1)</b>  t(15;17)(q22;q21)  t(8;21)(q22;q22)  inv(16)(p13q22)/t(16;16)(p13;q22)</p>
<p><b>Intermediate<sup>a</sup></b>  Entities not classified as favorable or adverse</p>
<p><b>Adverse<sup>b</sup></b>  abn(3q) [excluding t(3;5)(q21~25;q31~35)],  inv(3)(q21q26)/t(3;3)(q21;q26),  add(5q), del(5q), -5,  7, add(7q)/del(7q),  t(6;11)(q27;q23),  t(10;11)(p11~13;q23),  t(11q23) [excluding t(9;11)(p21~22;q23) and t(11;19)(q23;p13)]  t(9;22)(q34;q11),  -17/abn(17p),  Complex (≥4 unrelated abnormalities)</p>

a Patients with unknown cytogenetic risk per MRC classification, but fluorescence in situ hybridization (FISH) results indicating they do not have favorable risk should be stratified together with patients with intermediate cytogenetic risk

b Excluding cases with favorable karyotype

Adapted from Grimwade et al. ([Grimwade 2010](#))



## APPENDIX E: RESPONSE CATEGORIES

Term	Definition (all criteria must be met unless otherwise specified) <sup>a</sup>
Morphologic complete remission (CR)	Absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$ and platelets $\geq 100,000/\mu\text{L}$ without transfusions and/or exogenous growth factor support (i.e., no transfusion or exogenous growth factor within 7 days of assessment). Bone marrow with $< 5\%$ blasts No evidence of extramedullary disease
Morphologic complete remission with incomplete blood count recovery (CRi)	CRi(p) (morphologic CR with incomplete platelet recovery) Bone marrow with $< 5\%$ blasts Platelets $< 100,000/\mu\text{L}$ or $\geq 100,000/\mu\text{L}$ if patient transfused in last 7 days ANC $\geq 1000/\mu\text{L}$ without exogenous growth factor support No evidence of extramedullary disease
	CRi(n) (morphologic CR with incomplete neutrophil recovery) Bone marrow with $< 5\%$ blasts ANC $< 1000/\mu\text{L}$ or ANC $\geq 1000/\mu\text{L}$ with use of exogenous growth factors in last 7 days Platelets $\geq 100,000/\mu\text{L}$ without transfusions in last 7 days No evidence of extramedullary disease
Morphologic leukemia free state (mLFS)	Bone marrow with $< 5\%$ blasts No evidence of extramedullary disease Criteria for blood count recovery not met for CR or CRi
Partial remission (PR)	ANC $\geq 1000/\mu\text{L}$ and platelets $\geq 100,000/\mu\text{L}$ without transfusions and/or exogenous growth factor support (i.e., no transfusion or exogenous growth factor within 7 days of assessment). Bone marrow with 5% to 25% blasts and at least a 50% decrease in bone marrow blast percent from baseline No evidence of extramedullary disease
Antileukemic Effect	$> 25\%$ reduction of bone marrow blasts relative to baseline and criteria for PR not met
Stable Disease (SD)	Absence of CR, CRi, mLFS, PR, or antileukemic effect. Criteria for progressive disease (PD) not met
Progressive Disease (PD)	$> 25\%$ absolute rise in bone marrow blast percent from baseline or appearance of new extramedullary disease after 4 or more cycles of treatment. In patients with baseline bone marrow blasts $> 75\%$ , a 25% proportional (instead of absolute) increase in bone marrow blasts is considered PD.
Relapse from CR/CRi	Reappearance of blasts in the blood (unless consistent with regenerating bone marrow), or bone marrow ( $> 5\%$ ), or in any extramedullary site after achieving CR or CRi

<sup>a</sup> Modified from the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia (Cheson 2003).

## **APPENDIX F: NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION**

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

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

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

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

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

On-line source: [http://www.abouthf.org/questions\\_stages.htm](http://www.abouthf.org/questions_stages.htm)

## APPENDIX G: GUIDANCE ON CONTRACEPTION

### Acceptable Methods for Highly Effective Birth Control

Male patients, who are sexually active with a pregnant or breastfeeding woman, choose Option 1 or 2

Option 1: Male condom with spermicide and cervical cap

Option 2: Male condom with spermicide and diaphragm

Female patients who are of childbearing potential AND male patients who are sexually active with women of childbearing potential<sup>a</sup>, choose any TWO of the following methods:

- Hormonal methods of contraception (excluding progestin-only pills)
- Intrauterine device with failure rate <1%
- Tubal ligation
- Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
- A barrier method (male or female condom with spermicide, cervical cap with spermicide, diaphragm with spermicide)

<sup>a</sup> A woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological, physiological, or pharmacological causes.

### Unacceptable Methods of Contraception

Abstinence (including periodic abstinence)

No method

Withdrawal

Rhythm

Any barrier method without spermicide

Spermicide only

Progestin-only pills

Concomitant use of female and male condoms

## APPENDIX H: INVESTIGATOR SIGNATURE PAGE

### Investigator Statement and Signature

I have read the attached protocol entitled “A randomized, double-blind phase 3 study of vadastuximab talirine (SGN-CD33A) versus placebo in combination with azacitidine or decitabine in the treatment of older patients with newly diagnosed acute myeloid leukemia (AML).”

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

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Investigator Signature

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Date

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Investigator Name, Printed

## APPENDIX I: DOCUMENT HISTORY

Version	Date
Original	20-Jan-2016
Amendment 1	22-Mar-2016
Amendment 2	20-May-2016
Amendment 3	27-Mar-2017

## Summary of Changes in Amendment 1

Section(s)	Change	Rationale
Section 2.2, 2.4.2, 9.2.2.4, 9.3.5.2, and Synopsis	Duration of remission has been added as a secondary objective/endpoint of the study	To further characterize efficacy in this patient population
Section 3.1 and 9.3.10	The text has been revised as follows:  An IDMC will periodically monitor the trial for safety, <u>including SAEs and early mortality</u> , during the treatment period. See the IDMC Charter for details.	Clarification
Section 4.2	The following new exclusion criterion has been added:  <u>2. Patients who are medically fit and willing to receive standard intensive induction chemotherapy</u>	To clarify the older AML patient population who would receive low intensity therapy per standard of care
Section 4.2	The following new exclusion criterion has been added:  <u>14. Any other condition which, in the opinion of the investigator, would compromise patient safety or interfere with data interpretation.</u>	To further characterize the patient population who are eligible for enrollment
Section 5.3.3	The following language has been added:  <u>Refer to the azacitidine and decitabine package inserts or SmPC for complete instructions for dosing and administration.</u>	Clarification
Section 5.5.2	The text has been revised as follows:  Antimicrobial prophylaxis measures are strongly recommended, per institutional standard of care; <u>decisions regarding use and choice of antibiotics should be made by the individual institutions based on the prevailing organisms and their drug resistance patterns (de Naurois 2010; Freifeld 2011; Flowers 2013). The use of myeloid growth factors as part of supportive care for clinically significant neutropenia is recommended per the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines (Smith 2006; Fey 2013).</u>	Clarification

Section(s)	Change	Rationale
Section 7.7.2	RBC count and MCV have been added to the list of clinical laboratory tests	To further clarify the list of hematology tests to be performed
Section 9.3.1.9	The definition of the end of trial has been added	Clarification
Appendix B	Footnote f has been removed	To correct an error

## Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Section 1.2, 3.1.1, 4.1, and Synopsis	The lower age limit for study eligibility has been changed from $\geq 65$ years to $\geq 18$ years	To allow enrollment of all adult AML patients who are unfit for intensive chemotherapy, regardless of age
Section 4.1 and 4.2	The eligibility criteria have been revised to require females of childbearing potential to have a negative pregnancy test prior to enrollment as well as to use 2 effective contraceptive methods during the study. Female patients who are breastfeeding have also been excluded from enrollment	Pregnancy- and contraceptive-related restrictions and requirements have been added in accordance with the new lower age limit for the study
Section 5.5.2	The text has been revised as follows:  Antimicrobial prophylaxis measures are strongly recommended, per institutional standard of care; decisions regarding use and choice of antibiotics should be made by the individual institutions based on the prevailing organisms and their drug resistance patterns (de Naurois 2010; Freifeld 2011; Flowers 2013). The use of myeloid growth factors <u>are considered appropriate as part of supportive care for clinically significant neutropenia</u> <del>is recommended</del> per the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines (Smith 2006; Fey 2013) <u>and are strongly recommended as primary and/or secondary prophylaxis and as support of clinically significant neutropenia during treatment.</u>	To better emphasize the recommendations for prophylaxis of neutropenia for patients on the study
Section 6.2.1, 6.4, Appendix A	To require pregnancy testing at screening and end of treatment for females of childbearing potential	These assessments have been added in accordance with the new lower age limit for the study
Section 6.3.3 and 6.3.5	The text has been clarified to reflect the sampling schedule for PK on Days 5 and 7	Clarification
Section 9.3.1.7	The language has been modified as follows:  <u>The modified intent-to-treat (mITT) analysis set will include all patients from the ITT analysis set who receive any dose of blinded study treatment (vadastuximab talirine or placebo) or HMA. Patients will be included in the treatment group assigned at randomization regardless of the actual treatment received.</u>  The safety analysis set will include all patients who receive any <del>amount</del> <u>dose of blinded study treatment</u> (vadastuximab talirine or placebo) or HMA. Treatment group will be determined using the actual treatment received, regardless of the randomization treatment	To clarify the analysis sets for the study



Section(s)	Change	Rationale
	assignment. Patients receiving any dose of vadastuximab talirine will be grouped into the experimental arm. Patients who do not receive vadastuximab talirine but receive any dose of HMA will be grouped into the comparator arm.	
Section 9.3.5	The following language has been added:  <u>All efficacy endpoints will be analyzed using the ITT analysis set. Supplemental analyses will be performed using the mITT analysis set.</u>	To clarify the analysis sets for the study
Section 9.3.10	The language has been modified as follows:  An IDMC will periodically monitor the trial for safety, including SAEs and early mortality, during the treatment period. <del>See the IDMC Charter for details.</del> <u>During the periodical safety review, the IDMC will evaluate the 60-day mortality rates in the 2 treatment arms. The independent statistician will assist the IDMC to evaluate whether there is an increased risk of early death in the experimental arm and make appropriate recommendations to the sponsor.</u>  Two formal interim analyses for OS are planned for the study. The first interim analysis is for the purpose of futility testing and will be conducted when approximately 100 OS events have occurred (~30% of the targeted number of events). The second interim analysis is for superiority testing and will be conducted when approximately 200 OS events have occurred (~60% of the targeted number of events). The stopping boundaries will be determined using Lan-DeMets spending functions to simulate O'Brien-Fleming boundaries. Details will be provided in the SAP.  The IDMC will provide recommendations to the sponsor's Data Review Board as to appropriate study direction. The sponsor will remain blinded to treatment assignment. <u>See the IDMC Charter for details.</u>	To specify a blinded interim safety analysis to detect differences in early mortality between the arms

### Summary of Changes in Amendment 3

Section(s)	Change	Rationale
Sections 2, 3, 9, and Synopsis	Composite complete remission rate (CRc) has been changed from a secondary endpoint to an independent primary endpoint of the trial. The endpoints/objectives have also been re-ordered and revised to clarify that the MRD negative CRc rate will be compared between the treatment arms.	Achieving remission is considered clinically meaningful in the treatment of patients with AML (Cheson 2003). Long term follow-up data from the HMA combination arm of the vadastuximab talirine phase 1 study demonstrate that achieving a CRc, including either CR or CRi, predict for similarly favorable survival in this patient population (Fathi et al ASH 2016).
Section 3.2, Section 4.1 and Synopsis	Inclusion Criterion 5 has been revised to specify that patients 80 years and older must have an ECOG performance status of 0 or 1.	Historical data show that within the older AML population, outcomes are worse in the subset of patients who are age 80 years and older with poor performance status (Kantarjian 2010; Oran 2012). Age $\geq$ 80 years and a high degree of comorbidity were associated with an increased risk of early death and shorter median overall survival regardless of therapy received, including HMAs. Therefore, patients age 80 and older will be required to have an ECOG performance status of 0 or 1.
Section 4.1	Inclusion Criteria 7 and 8 have been revised to clarify contraceptive requirements for male and female patients as well as clarify restrictions on breastfeeding, pregnancy, and sperm/ova donation.	Clarification and to ensure patient safety per the EU Clinical Trial Facilitation Group's (CTFG) "Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials."
Section 4.2	The following new exclusion criteria have been added: <ul style="list-style-type: none"> <li>• <u>Patients with supplemental oxygen requirement or resting oxygen saturation of &lt;90%</u></li> <li>• <u>History of clinically significant chronic liver disease (e.g. liver cirrhosis) and/or ongoing alcohol abuse</u></li> </ul>	To further enhance trial population homogeneity, ensure patient safety, and facilitate interpretation of outcomes.

Section(s)	Change	Rationale
Section 4.2 and Synopsis	<p>Exclusion Criterion 9 (previously Criterion 7) has been revised as follows:</p> <p><del>Second malignancy requiring active systemic therapy within 1 year (except for hormonal/anti-hormonal treatment, e.g., prostate or breast cancer).</del></p> <p><u>Concurrent active malignancy other than nonmelanoma skin cancer or carcinoma in situ of the following: bladder, stomach, colon, cervix, endometrium, melanoma, or breast. Patients with previous malignancies are eligible if the malignancy has been confined and surgically resected (or treated with other modalities) with curative intent. Any active systemic therapy must have been completed &gt;1 year from enrollment (except for hormonal/anti-hormonal treatment, e.g. breast cancer).</u></p>	Clarification to further enhance trial population homogeneity and facilitate interpretation of outcomes.
Section 4.2 and Synopsis	<p>Exclusion Criterion 17 (previously Criterion 15) has been revised as follows:</p> <p><u>Significant history of pulmonary, renal, neurologic, psychiatric, endocrine, metabolic, immunologic, hepatic, cardiovascular disease, or Any other condition which, in the opinion of the investigator, would adversely affect participation in this study</u> compromise patient safety, or interfere with data interpretation.</p>	To further enhance trial population homogeneity, ensure patient safety, and facilitate interpretation of outcomes.
Section 4.3 and Appendix G	Section 4.3 has been added to define childbearing potential as it pertains to trial eligibility. Appendix G has been added to provide guidance on contraception.	Clarification and to ensure patient safety per the EU CTFG “Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials.”

Section(s)	Change	Rationale
Section 5.2.3	<p>The dose modification section has been revised as follows:</p> <ul style="list-style-type: none"> <li>• Rules have been added for dose modifications in the event of laboratory evidence of hepatic toxicity (elevated AST, ALT, or total bilirubin)</li> <li>• Instructions have been added to discontinue treatment for delays of &gt;56 days after dose reduction unless approved by the medical monitor</li> <li>• The rules for non-hematologic toxicity (with the exception of hepatic toxicity) have been revised to change the period of required treatment delay for <math>\geq</math> Grade 3 events from 28 days to 14 days and to remove the stipulation that <math>\geq</math> Grade 3 events must be clinically significant or symptomatic to invoke treatment delay</li> </ul>	To ensure patient safety.
Section 5.5.3	<p>The prohibited concomitant medications section has been revised as follows:</p> <p>Patients may not receive other investigational drugs, immunosuppressive medications (with the exception of the medications listed in Section 5.5.2), <del>or</del> non-study systemic anti-neoplastic therapy, <u>or allo-SCT</u> during the treatment period.</p> <p><u>If patients become candidates for allo-SCT after enrollment, blinded study treatment must be discontinued at least 30 days prior to initiation of the preparative regimen for allo-SCT.</u></p>	To clarify that allogeneic stem cell transplantation is prohibited during the treatment period and within 30 days of the last dose of blinded study treatment.
6.3.1 and Appendix A	A pregnancy test has been added on Day 1 of each cycle of study treatment.	To ensure patient safety per the EU CTFG “Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials.”
6.2.1 and Appendix A	A pulse oximetry test has been added at baseline to assess oxygen saturation level at room air.	To ensure patient safety.
6.3.3, 6.3.5, 7.7.6, 9.3.9.5, Appendix A	Measurement of vital signs has been added pre- and within 30 minutes post-blinded study treatment administration.	To ensure patient safety.
6.5	The follow up assessments section has been revised for clarity and to provide information regarding follow-up of adverse events of special interest.	To provide clarity and ensure patient safety.

Section(s)	Change	Rationale
7.7.1.4	A new section has been added to define hepatobiliary serious adverse events, including cases of sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD), as adverse events of special interest and to provide instructions on reporting of these events.	To ensure patient safety.
Throughout protocol	Additional minor clarifications/edits and administrative changes have been made.	To improve clarity and ensure consistency throughout the protocol as well as to make administrative changes.