OncoVerity, Inc

Clinical Protocol

Protocol Title

A Phase 2 Study of Cusatuzumab Plus Azacitidine in Patients With Newly Diagnosed Acute Myeloid Leukemia who are not Candidates for Intensive Chemotherapy

Protocol CULM20236; Phase 2
AMENDMENT 4

OV-1001* (Cusatuzumab)

*Previously JNJ-74494550 (Protocol 74494550AML2001)

US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

EudraCT NUMBER: 2019-000473-23

Status: Approved
Date: 13 Jun 2023
Prepared by: OncoVerity, Inc

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document	Date
Amendment 4	13 Jun 2023
Amendment 3	30 September 2021
Amendment 2	19 August 2020
Amendment 1	22 October 2019
Original Protocol	18 March 2019

Amendment 4 (19 May 2023)

Overall Rationale for the Amendment: After 22 Oct 2021 (after the primary endpoint analysis had been completed), subjects who are still benefiting from study treatment can continue to receive study treatments and will have a reduced schedule of assessments.

Section Number and Name	Description of Change	Brief Rationale
Throughout the protocol	Updates to the program number (from JNJ-74494550 to OV-1001), study number (from AML2001 to CULM20236), and study sponsor (from Janssen Research and Development to OncoVerity Inc.).	Updating for a new sponsor, namely OncoVerity, Inc..

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2 Study of Cusatuzumab Plus Azacitidine in Patients With Newly Diagnosed Acute Myeloid Leukemia who are not Candidates for Intensive Chemotherapy.

CD70 is a cell surface antigen normally expressed in a small subset of activated B- and T- lymphocytes and is involved in lymphocyte differentiation and survival signaling upon binding to its receptor, CD27. CD70 is over-expressed in several tumor types, often together with CD27 in hematological malignancies suggesting its involvement in proliferation and survival of the malignant cells. Over 95% of acute myeloid leukemia (AML) blasts harvested from newly diagnosed AML patients expressed CD70 on the cell surface. Cusatuzumab (OV-1001) is a humanized monoclonal antibody of camelid origin, binding with high affinity to human CD70. Cusatuzumab has been modified to induce enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) for therapeutic use in patients with cancer.

Primary Objective

The primary objective of this study is to determine the complete response (CR) rate of 2 dose levels of cusatuzumab in combination with azacitidine in participants with previously untreated AML who are not eligible for intensive chemotherapy.

Hypothesis

The primary hypothesis of this study is that the combination of cusatuzumab at doses of 10 mg/kg or 20 mg/kg with azacitidine has a CR rate of no less than 35% in patients with previously untreated AML who are not eligible for intensive chemotherapy.

OVERALL DESIGN

Up to approximately 150 participants will be treated in this randomized study of 2 dose levels of cusatuzumab in combination with azacitidine in patients with previously untreated AML who are not eligible for intensive chemotherapy. The study will consist of 2 parts: the purpose of Part 1 is to select a dose based on the totality of the data; the purpose of Part 2 is to evaluate and confirm the efficacy and safety of the selected dose level. NOTE: Part 2 of the study will not be conducted because further development of this regimen (cusatuzumab in combination with azacitidine) in patients with unfit AML will not be pursued due to the evolving treatment landscape in AML.

After 22 Oct 2021, ongoing subjects (on treatment or in follow-up) will be treated and assessed according to a reduced schedule of assessment (Table 1A).

TREATMENT GROUPS AND DURATION

In Part 1 of the study, participants will be randomized in a 1:1 ratio to receive cusatuzumab and azacitidine in 1 of the following 2 dosing regimen groups:

- Group A: Azacitidine 75 mg/m^2 SC or IV on Day 1 through Day 7, cusatuzumab 10 mg/kg IV on Day 3 and Day 17 of each 28-day cycle
- Group B: Azacitidine 75 mg/m^2 SC or IV on Day 1 through Day 7, cusatuzumab 20 mg/kg IV on Day 3 and Day 17 of each 28-day cycle

Participants will be treated until disease progression, relapse, unacceptable toxicity, or withdrawal due to investigator discretion or withdrawal of consent. The Follow-up Phase will begin once a participant discontinues study intervention, and will continue until death, loss to follow up, consent withdrawal for

study participation, or study end, whichever occurs first. The end of study will be reached when all subjects have completed or discontinued study treatment. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final participant visit at the study site, in the time frame specified in the Clinical Trial Agreement.

EFFICACY EVALUATIONS

Disease evaluations will include peripheral blood and bone marrow assessments and will be conducted per local laboratory as indicated in the Schedule of Activities. Disease status will be evaluated according to European Leukemia Network (ELN) Response Criteria in AML (2017). Survival status and subsequent anticancer therapy will also be collected.

PHARMACOKINETIC EVALUATIONS

Plasma and serum samples will be analyzed to determine concentrations of azacitidine and cusatuzumab, respectively. Cusatuzumab concentrations in bone marrow may also be determined.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Pharmacodynamic biomarker tests will include evaluation of the change in soluble CD27 (sCD27) level, change of CD70 and CD27 expression levels, decrease of blasts and leukemia stem cells in whole blood and bone marrow by flow cytometry, and expression of CD70-CD27 signaling and leukemic stem cell-related genes by transcriptome analysis. Biomarker tests will also evaluate the mechanism of action of cusatuzumab by flow cytometric or time of flight mass cytometry (CyTOF) assessment of natural killer (NK), T- and B-cells. Minimal/measurable residual disease will be evaluated by flow cytometry and molecular approaches according to ELN guidance 2018.

SAFETY EVALUATIONS

The safety of cusatuzumab will be assessed by physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, clinical laboratory tests, vital signs, and adverse event monitoring.

STATISTICAL METHODS

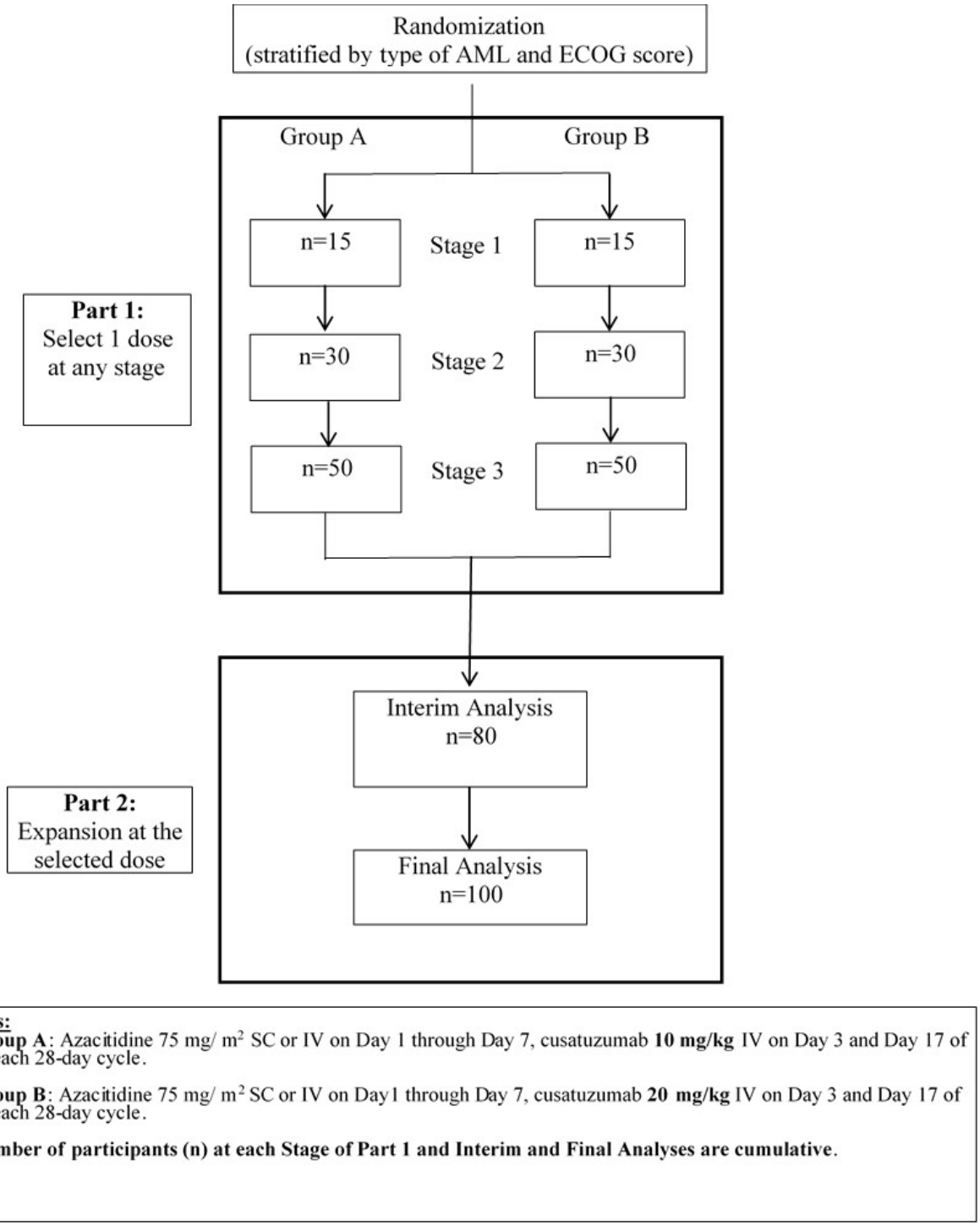
Part 1 of the study will utilize a 3-stage monitoring approach to determine, at each stage and for each dose group, if the observed CR rate warrants the respective dose to be continued into the next stage or into Part 2 of the study. Only 1 dose will be selected to continue to Part 2. Participants will be enrolled into Part 2 at the selected cusatuzumab dose until a cumulative total of 100 participants have been treated with the selected dose from Part 1 and Part 2. The study has a >90% power to reject the null hypothesis of a CR rate of 20% under the alternative hypothesis of 35% for a total of 100 participants (from Part 1 and Part 2) at the selected dose level. This sample size is based on the single-arm Wilson Score test without continuity correction at an overall 1-sided type 1 error rate <2.5%.

1.2. Schema

A diagram of the study design is provided in Figure 1.

NOTE: Part 2 of the study will not be conducted because further development of this regimen (cusatuzumab in combination with azacitidine) in patients with unfit AML will not be pursued due to the evolving treatment landscape in AML.

Figure 1: Schema for Study CULM20236



Notes:

- **Group A**: Azacitidine 75 mg/ m^2 SC or IV on Day 1 through Day 7, cusatuzumab **10 mg/kg** IV on Day 3 and Day 17 of each 28-day cycle.
- **Group B**: Azacitidine 75 mg/ m^2 SC or IV on Day1 through Day 7, cusatuzumab **20 mg/kg** IV on Day 3 and Day 17 of each 28-day cycle.
- **Number of participants (n) at each Stage of Part 1 and Interim and Final Analyses are cumulative**.

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities Up to 22 Oct 2021

NOTE: As of Amendment 3: After 22 Oct 2021, subjects will no longer follow this SoA. Subjects will be treated and assessed according to Table 1A.

	Screening	**Randomization**	**Treatment**		**Follow-up**
Study Procedure	Within 28 days of randomization	Within 72 hours of first dose	Azacitidine/ cusatuzumab combination therapy (28-day cycle) Cycle 1 – EOT	EOT[a]	30 days (±3 days) after last dose of study treatment and then every 3 months thereafter (±7 days)[b]
Screening/ Administrative					
Informed consent[c]	X				
Demographics/ medical history	X				
Cytogenetic testing/ Mutational analysis	X[d]				
Inclusion/exclusion criteria[e]	X	X			
Study Intervention Administration					
Randomization		X			
Pre-medications[f]			X		
Azacitidine 75 mg/m^2 SC or IV[e]			Day 1 to Day 7 of each 28-day cycle		
Cusatuzumab IV infusion at selected dose[f]			Day 3 and Day 17 of each 28-day cycle (+2 days)		
Efficacy Assessments					
Disease evaluation[g]	X[h]		Every other cycle, starting at Cycle 1, (between Day 21 up to and including Day 1 of the next cycle) until CR or progressive disease. Once CR is achieved, disease evaluation can be performed every 4th cycle until relapse. Once CR without MRD is achieved, a repeat bone marrow examination to confirm should be performed at least 4 weeks later. In cases of cycle delays, timing of disease evaluations should be performed per protocol at the end of the specified odd cycle.	X	
Bone marrow aspirate[i]	Within 7 days of Cycle 1/ Day 1		At every disease evaluation	X	
Evaluation of extramedullary disease[j]	X		At every disease evaluation as needed	X	
Transfusion status	X		At every disease evaluation	X	

	Screening	Randomization	Treatment		Follow-up
Study Procedure	Within 28 days of randomization	Within 72 hours of first dose	Azacitidine/ cusatuzumab combination therapy (28-day cycle) Cycle 1 – EOT	EOT[a]	30 days (±3 days) after last dose of study treatment and then every 3 months thereafter (±7 days)[b]
Survival status/subsequent therapy/ other malignancies				X	X[k]
Safety Assessments (See Section 8)					
Adverse events and concomitant therapy	X		X	X	X
Physical Examination height and weight	X		Day 1 of each cycle (height is measured at screening only)	X	
Vital signs[l]	X		Days 1, 3, and 17 of each cycle	X	
ECOG assessment	X		Day 1 of each cycle	X	
12-lead ECG[l]	X		For participants with baseline cardiac disease, perform additional ECG every other cycle (at same time as disease evaluation). For other participants, only if clinically indicated		
Spirometry	X (only for participants with baseline pulmonary disease)		For participants with baseline pulmonary disease, perform spirometry every 4th cycle at same time as disease evaluation. For other participants, only if clinically indicated		
Medical resource utilization[m]	Continuous from the time of signing of the ICF until 30 days after the last dose of study intervention				
Clinical Laboratory tests (See Appendix 2, Section 10.2)					
Hematology, including peripheral blood blast counts	X		During Cycle 1: hematology should be checked weekly. For all other cycles, check on Day 1 and Day 17 of each cycle and with each disease evaluation.[n] If clinically indicated, monitoring should be more frequent.	X	
Chemistry	X		During Cycle 1: chemistry should be checked weekly. For all other cycles, check on Day 1 and Day 17 of each cycle and with each disease evaluation.[n] If clinically indicated, monitoring should be more frequent.	X	
Pregnancy test for women of childbearing potential	X		X	X[o]	
Hepatitis and HIV[p]	X				
Pharmacodynamics and Biomarkers (whole blood/ PBMC/ serum/ bone marrow sample collection)					
PD/ Biomarker testing (See Table 2)	Within 7 days of Cycle 1/ Day 1		See Table 2 for Sampling Schedule		
Pharmacokinetics (Bone marrow and Peripheral blood)					
PK testing (See Table 3 and Table 5)	Within 7 days of Cycle 1/ Day 1		See Table 3 for Sampling Schedule for first 50 participants (25 per group) and Table 5 for participants randomized after the 50th		

	Screening	Randomization	Treatment		Follow-up
Study Procedure	Within 28 days of randomization	Within 72 hours of first dose	Azacitidine/ cusatuzumab combination therapy (28-day cycle) Cycle 1 – EOT	EOT[a]	30 days (±3 days) after last dose of study treatment and then every 3 months thereafter (±7 days)[b]
Patient-reported outcomes (PRO)[q]					
Fact-Leu			Day 1 of each cycle	X	Only at first visit[k]
EQ-5D-5L			Day 1 of each cycle	X	Only at first visit[k]

AML= acute myeloid leukemia; CR= complete response; CRh= <5% blasts in the bone marrow, no evidence of disease and partial recovery of platelets to >50,000/µL and absolute neutrophil count >500/µL; CRi= complete response with incomplete blood count recovery; ECG= electrocardiogram; ECOG= Eastern Cooperative Oncology Group status score; EOT= end of treatment; HIV= human immunodeficiency virus; ICF= informed consent form; IV= intravenous; MRD= minimal residual disease; PK= pharmacokinetics; PRO= patient-reported outcomes; SC= subcutaneous

a. The End of Treatment Visit must occur in person within approximately 7 days of treatment discontinuation.
b. As per Section 8.3.1, all adverse events will be reported until 30 days after the last dose of study intervention or until the start of subsequent anti-AML therapy, if earlier.
c. ICF must be signed before first study-related activity is performed.
d. Assessment of mutational status must be performed and must include testing for **all** mutations listed in Appendix 10. Mutational analyses should be performed on bone marrow collected at screening. Central and/or local testing is acceptable. Local, standard-of-care assessment of mutational status obtained prior to the ICF signing will be accepted in lieu of a repeat assessment on screening marrow, provided that it includes testing for all mutations outlined in Appendix 10. Left over fresh or frozen bone marrow samples may be requested for central mutational analysis if all tests are not performed by the local study site.
e. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documents in Appendix 3.
f. See Section 6.1 and Section 6.1.1 for dosing schedule and premedications. When cusatuzumab and azacitidine are scheduled to be administered together, azacitidine should be administered first. It is recommended that there is at least 30 minutes waiting time between the end of azacitidine administration and the start of the cusatuzumab infusion.
g. Evaluation includes bone marrow evaluation (bone marrow aspirate preferred for assessment of blast %), hematology with differential, transfusion assessment, and assessment for extramedullary disease per local standard of care. Results of MRD testing will be provided by the Sponsor when appropriate. For participants who discontinue study treatment without disease progression, disease evaluations should continue with the same frequency as during study treatment until disease progression.
h. Obtain 2 to 3 peripheral blood blast counts during screening
i. A bone marrow aspirate should be performed for the disease assessment (for bone marrow blasts) within 7 days of first dose (or Cycle 1 Day 1). Once a bone marrow aspirate is performed, the sample must be sent to central laboratory within 48 hours for biomarker and PK testing. In case of a dry tap, a biopsy may also be utilized for disease assessment. See Table 2 for bone marrow biomarker sampling and Table 3 for bone marrow PK sampling. Any unscheduled bone marrow assessments must be reported.
j. Evaluation for extramedullary disease required only for participants with suspicion of or known extramedullary AML disease
k. Assessments may occur via telephone contact.
l. Vital Signs: heart rate, blood pressure (monitor with same method and position [sitting or supine] throughout study), respiratory rate, and temperature to be performed prior to administration of any study intervention. If blood sampling or vital sign measurement is scheduled for the same timepoint as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw. See Section 8.2.2
m. Information on health care needs during treatment (eg, physiotherapist) to be collected by study staff.
n. Samples may be obtained within 24 hours of the Day 1 and Day 17 visits.
o. Pregnancy testing to also be performed for women of childbearing potential 1 month after last dose of study treatment.
p. Laboratory testing for hepatitis and HIV at screening is to be performed for all participants.
q. PROs should be performed before dosing and before any study tests or procedures or consultations are conducted when possible.

Table 1A: Schedule of Activities After 22 Oct 2021

	Treatment		Follow-up
Study Procedure	Azacitidine/ cusatuzumab combination therapy (28-day cycle) Cycle 1 – EOT	EOT[a]	30 days (±3 days) after last dose of study treatment and then every 3 months thereafter (±7 days)[b]
Study Intervention Administration			
Pre-medications[c]	X		
Azacitidine 75 mg/m^2 SC or IV[d]	Day 1 to Day 7 of each 28-day cycle		
Cusatuzumab IV infusion at selected dose[c]	Day 3 and Day 17 of each 28-day cycle (+2 days)		
Efficacy Assessments			
Disease evaluation[d]	Every other cycle, starting at Cycle 1, (between Day 21 up to and including Day 1 of the next cycle) until CR or progressive disease. Once CR is achieved, disease evaluation can be performed every 4th cycle until relapse. Once CR without MRD is achieved, a repeat bone marrow examination to confirm should be performed at least 4 weeks later. In cases of cycle delays, timing of disease evaluations should be performed per protocol at the end of the specified odd cycle.	X	
Bone marrow aspirate[e]	At every disease evaluation	X	
MRD[e]	Bone marrow: Every 4 cycles following CR and every 2 cycles following CRi/CRh (collected between Day 21 up to and including Day 1 of the next cycle) Whole Blood: Every 2 cycles following CR/CRi/CRh on Day 1	X	
Evaluation of extramedullary disease[f]	At every disease evaluation as needed	X	
Transfusion status	At every disease evaluation	X	
Survival status/subsequent therapy/ other malignancies		X	X[g]
Safety Assessments (See Section 8)			
Adverse events and concomitant therapy	X	X	X
Weight	Day 1 of each cycle	X	
Clinical Laboratory tests (See Appendix 2, Section 10.2)			
Hematology, including peripheral blood blast counts	Beyond cycle 1, check on Day 1 and Day 17 of each cycle, with each disease evaluation and as clinically indicated.	X	
Chemistry	With each disease evaluation and as clinically indicated	X	
Pregnancy test for women of childbearing potential	X	X[h]	

AML= acute myeloid leukemia; CR= complete response; CRh= CR with partial hematological recovery (<5% blasts in the bone marrow, no evidence of disease and partial recovery of platelets to >50,000/µL and absolute neutrophil count >500/µL); CRi= complete response with incomplete blood count recovery; IV= intravenous; MRD= minimal residual disease; SC= subcutaneous

a. The End of Treatment Visit must occur in person within approximately 7 days of treatment discontinuation.
b. As per Section 8.3.1, all adverse events will be reported until 30 days after the last dose of study intervention or until the start of subsequent anti-AML therapy, if earlier.
c. See Section 6.1 and Section 6.1.1 for dosing schedule and premedications. When cusatuzumab and azacitidine are scheduled to be administered together, azacitidine should be administered first. It is recommended that there is at least 30 minutes waiting time between the end of azacitidine administration and the start of the cusatuzumab infusion.
d. Evaluation includes bone marrow evaluation (bone marrow aspirate preferred for assessment of blast %), hematology with differential, transfusion assessment, and assessment for extramedullary disease per local standard of care. In case of a dry tap, a biopsy may be utilized for disease assessment. For participants who discontinue study treatment without disease progression, disease evaluations should continue with the same frequency as during study treatment until disease progression or start of subsequent therapy, whichever occurs first. Any unscheduled bone marrow assessments must be reported.

	Treatment		Follow-up
Study Procedure	Azacitidine/ cusatuzumab combination therapy (28-day cycle)	EOT[a]	30 days (±3 days) after last dose of study treatment and then every 3 months thereafter (±7 days)[b]
	Cycle 1 – EOT		

e. Once a bone marrow aspirate is performed, the sample must be sent to central laboratory within 48 hours for MRD analysis by flow cytometry. Results of MRD testing will be provided by the Sponsor when appropriate.
f. Evaluation for extramedullary disease required only for participants with suspicion of or known extramedullary AML disease
g. Assessments may occur via telephone contact.
h. Pregnancy testing to also be performed for women of childbearing potential 1 month after last dose of study treatment.

Table 2: Schedule of Pharmacodynamic and Biomarker Evaluations

Note: After 22 Oct 2021, the assessments below will not be performed except for MRD, which is included in Table 1A.

Study Day	Dose	Time (window)	Flow cytometry/ CyTOF	Flow cytometry/CyTOF/MRD[a]	Cytokines	Protein Quantification	Gene expression	MRD[a]	DNA sequencing
Sample			**Whole blood**	**Bone marrow aspirate**	**Serum[b]**	**Serum**	**Whole blood**	**Whole blood**	**Bone marrow aspirate**
Screening[c]				X				X	X
Cycle 1 / Day 1	Azacitidine	Predose	X		X	X	X		
Cycle 1/ Day 2	Azacitidine	Postdose	X			X	X		
Cycle 1 / Day 3	Azacitidine/ cusatuzumab	Predose			X				
	Cusatuzumab	EOI (+10 min)			X				
Cycle 1 / Day 3	Cusatuzumab	6 hr after EOI (± 30 min)			X				
Cycle 1 / Day 4	Cusatuzumab	24 hr after EOI (± 2 hrs)			X				
Cycle 1 / Day 7	Cusatuzumab	96 hr after EOI (± 2 hrs)	X			X	X		
Cycle 1 / Day 17	Cusatuzumab	Predose	X			X	X		
Every 2 cycles following CR/CRi/CRh on Day 1								X	
At every disease evaluation			X	X		X	X		
EOT			X	X		X	X	X	

CyTOF= time of flight mass cytometry; EOI= end of infusion; MRD= minimal/measurable residual disease; PBMC= peripheral blood mononuclear cells

a. Bone marrow aspirate samples will be analyzed by flow cytometry; bone marrow aspirate and blood samples will be stored for analysis in the future by molecular methods.
b. Cytokine testing for the first 30 participants only. Additional serum samples will be collected from a participant when a Grade 3 or higher infusion-related reaction event is observed. If the infusion-related reaction event coincides with the serum samples that are already being collected, then additional samples do not need to be collected.
c. Screening samples will be taken within 7 days of Cycle 1/ Day 1.

Table 3: Schedule of Pharmacokinetic Evaluations for the First 50 Participants (approximately 25 for each dose; intensive PK sampling)

Note: After 22 Oct 2021, no pharmacokinetic samples will be collected.

Study Cycle and Day	Time (Window)	Serum Cusatuzumab PK	Whole Blood RO[a]	Serum ADA	Bone Marrow Cusatuzumab PK[b]
Screening					X
Cycle 1 Day 3	Predose[c]	X	X	X	
	EOI postdose (+10 min)	X	X		
Cycle 1 Day 4	24 hours postdose (±2 hours)	X	X		
Cycle 1 Day 7	96 hours postdose (±6 hours)	X	X		
Cycle 1 Day 10	168 hours postdose (±12 hours)	X	X		
Cycle 1 Day 17	Predose[c]	X	X	X	
	EOI postdose (+10 min)	X	X		
Cycle 2 Day 3	Predose[c]	X	X	X	
	EOI postdose (+10 min)	X	X		
Cycle 2 Day 17	Predose[c]	X	X	X	
	EOI postdose (+10 min)	X	X		
Cycle 3 Day 3 and Cycle 4 Day 3	Predose[c]	X	X	X	
	EOI postdose (+10 min)	X	X		
Cycle 3 Day 17 and Cycle 4 Day 17	Predose[c]	X	X		
	EOI postdose (+10 min)	X	X		
Cycle 3 Day 21 to Cycle 4 Day 1	At disease evaluation	X			X
Cycle 5 Day 3	Predose[c]	X		X	
	EOI postdose (+10 min)	X			
Cycle 5 Day 21 to Cycle 6 Day 1	At disease evaluation	X			X
Odd cycles ≥ Cycle 7 Day 3	Predose[c]	X		X	
	EOI postdose (+10 min)	X		X	
EOT	(±7 days)	X		X	

ADA=anti-drug antibody; EOI=end-of-infusion; EOT=end-of-treatment; PK=pharmacokinetics; RO=receptor occupancy

i. Whole blood RO: For first 4 cycles only, dependent on assay availability.
j. Bone marrow concentration will only be evaluated in approximately 8 participants in each cohort. Bone marrow aspirates should be collected at disease evaluation. A blood sample for serum PK should also be collected at the same time.

Predose samples may be collected within 2 hours before dosing unless otherwise indicated.

Table 4: Schedule of Pharmacokinetic Evaluations for Azacitidine[a]

Note: After 22 Oct 2021 no pharmacokinetic samples will be collected.

Study Cycle and Day[a]	Time (Window)
Cycle 1 Day 1	Predose[b]
	EOI postdose (+10 min)
	30 min postdose (±5 min)
Cycle 1 Day 3	Predose[b]
	EOI postdose (+10 min)
	30 min postdose (±5 min)
Cycle 3 Day 3	Predose[b]
	EOI postdose (+10 min)
	30 min postdose (±5 min)
EOT	(±7 days)

EOI= end of infusion; EOT= end of treatment

a. Azacitidine PK samples are to be collected from at least 20 participants from each azacitidine administration group (IV or SC). Whichever route of administration (IV or SC) is given for the first dose should be continued for all subsequent doses whenever possible in participants selected to have samples collected for azacitidine PK.
b. Cusatuzumab pre-dose samples may be collected within 2 hours before dosing unless otherwise indicated.

Table 5: Schedule of Pharmacokinetic Evaluations for Participants Randomized after the 50th Participant (sparse PK sampling)

Note: After 22 Oct 2021, no pharmacokinetic samples will be collected.

Study Cycle and Day	Time (Window)	Serum Cusatuzumab PK	Whole Blood RO[a]	Serum ADA
Screening				
Cycle 1, 2, 3 and 4 Day 3	Predose[b]	X	X	X
	EOI postdose (+10 min)	X	X	
Cycle 1, 2, 3 and 4 Day 17	Predose[b]	X	X	X
	EOI postdose (+10 min)	X	X	
Odd cycles ≥Cycle 5 Day 3	Predose[b]	X		X
	EOI postdose (+10 min)	X		
EOT	(±7 days)	X		X

a. For first 4 cycles only
b. Cusatuzumab pre-dose samples may be collected within 2 hours before dosing unless otherwise indicated.

2. INTRODUCTION

2.1. Study Rationale

This study is intended to evaluate cusatuzumab plus azacitidine in patients with previously untreated AML who are not candidates for intensive chemotherapy and are generally older or with medical comorbidities. As of January 24, 2019, cusatuzumab has been studied in the same patient population in 29 patients with AML in study ARGX-110-1601. In the Phase 1 portion of the Phase 1/2 dose escalation study of 1 to 20 mg/kg cusatuzumab plus azacitidine a maximum tolerated dose was not reached and combination therapy resulted in a CR rate of 67% (n=12). Higher doses of cusatuzumab (10 and 20 mg/kg) achieved target drug levels in the peripheral blood and bone marrow and lower rates of anti-drug antibodies (ADA) than at lower dose levels (Section 2.2.2).

This two-part Phase 2 study, CULM20236, will evaluate the safety and efficacy of 2 dose levels of cusatuzumab, 10 mg/kg and 20 mg/kg, in combination with azacitidine, in participants with previously untreated AML who are not candidates for intensive chemotherapy. Part 1 of the study is to select a dose and Part 2 will further characterize the efficacy and safety of cusatuzumab at the selected dose in combination with azacitidine.

2.1.1. Study Design Rationale

Safety and tolerability of cusatuzumab monotherapy initially were described in the first-in-human (FIH) Phase 1 dose escalation study ARGX-110-1201 of up to a dose of 10 mg/kg once every 3 weeks in adult subjects with advanced (solid tumor and hematological) malignancies. In a subsequent open-label non-randomized study in AML or high-risk myelodysplastic syndrome (MDS) patients who are not candidates for intensive chemotherapy, study ARGX-110-1601 investigated the safety and tolerability of escalating doses of cusatuzumab at 1, 3, 10, and 20 mg/kg given once as monotherapy followed by every 2 weeks in combination with standard doses of azacitidine. As of 24 January 2019, 12 adult subjects with AML have received the combination of cusatuzumab and a standard dose of azacitidine in the Phase 1 portion of the study and 17 additional AML subjects have been enrolled in an expansion cohort of cusatuzumab 10 mg/kg in combination with azacitidine in the Phase 2 portion of the study. No patients with MDS have been enrolled.

Data from the Phase 1 portion of Study ARGX-110-1601 (n=12) demonstrated that cusatuzumab up to 20 mg/kg every 2 weeks in combination with azacitidine has a safety profile consistent with azacitidine toxicity with the addition of infusion-related reactions (IRRs). Combination therapy demonstrated a CR rate of 67%, a promising result in this patient population (Section 2.2.2).

This study, CULM20236, will evaluate 2 doses of cusatuzumab, 10 mg/kg and 20 mg/kg, in combination with standard dose azacitidine in participants with AML who are not candidates for intensive chemotherapy to determine a dose level (Part 1) at which to further evaluate and confirm the response rate, other efficacy endpoints, tolerability, and PK/PD (Part 2). NOTE: Part 2 of the study will not be conducted because further development of this regimen (cusatuzumab in combination with azacitidine) in patients with unfit AML will not be pursued due to the evolving treatment landscape in AML. Up to approximately 150 participants will be enrolled for the entire

study. Randomization will be implemented for Part 1 of the study and will be stratified by type of AML (de novo versus secondary AML) and ECOG score (0-1 versus 2). A 3-stage monitoring approach will be utilized in Part 1 so that a dose may be selected early (see Schema in Figure 1).

The term "Sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document. The term "participant" throughout the protocol refers to the common term "subject" enrolled in this study. The term “study intervention” throughout the protocol refers to either study drug.

2.1.2. Rationale for the Selected Patient Population

Five-year survival in older patients with AML is less than 5% and has not improved significantly in the last few decades, especially in those over 75 years of age.[25] More effective therapies are clearly needed. Multiple clinical studies are underway combining novel therapy with azacitidine in the hope of achieving better clinical outcomes than with azacitidine alone.

The study population of this study as outlined in the inclusion/exclusion criteria (Section 5) are consistent with published guidelines[8,18] and other recent clinical studies that define this unfit population. Although choice of therapy in patients with AML is dependent on the patient’s age, comorbidities, and patient/ physician preference,[13,27] low intensity therapy with hypomethylating agents such as azacitidine is an accepted standard of care option in the patient population included in this study.

2.1.3. Rationale for Combination Treatment With Cusatuzumab Plus Azacitidine

Riether (2017)[23] demonstrated that >95% of AML blasts harvested from newly diagnosed AML patients expressed CD70 on the cell surface. In 70% to 95% of these samples, expression of CD70 and CD27, its ligand, was observed. Additionally, significantly elevated soluble CD27 levels (sCD27), resulting from ligation of CD70 to its receptor and subsequent cleavage by a cell surface protease were observed. More extensive transcriptome studies revealed a role for CD70-CD27 signaling in proliferation and stem cell maintenance of AML blast populations. Ex vivo and in vivo models demonstrated a pathological role for CD70-CD27 signaling in maintaining the stemness character of the AML blast population.

Transient treatment (2 weeks) with an anti-human CD70 blocking antibody significantly reduced colony formation in primary and secondary replating experiments and in secondary transplantation in AML patient xenografts, indicating that treatment affected the leukemic stem cells (LSC).[23] This is particularly relevant as LSCs are responsible for minimal residual disease (MRD) and AML relapse.[9,21,22] Notably, normal hematopoietic stem cells lack CD70 expression.[10] Therefore, effective targeting of CD70 should result in the ablation of leukemic blasts and LSC while sparing normal hematopoiesis.

Cusatuzumab is an anti CD70 antibody that binds with high affinity to CD70, thereby blocking interaction with CD27 (see Section 2.2.2). This blockade interferes with anti-apoptotic CD70-CD27 signaling, likely hampering tumor growth. CD70 targeting by cusatuzumab demonstrated efficacy in patients with AML possibly by blocking proliferation of AML blasts,

depleting CD70-positive AML blasts via enhanced ADCC (Potelligent® technology), reducing the stemness of AML blasts and targeting leukemic stem cells and driving them towards myeloid differentiation.

Azacitidine and decitabine are inhibitors of DNA methyltransferases known to upregulate gene expression by promoter hypomethylation. Hypomethylating agents (HMA) are the standard of care for first line treatment in patients with AML who are not candidates for intensive chemotherapy. CD70 expression has also been shown to be increased on AML stem/progenitor cells from patients treated with HMAs suggesting hypomethylating agents upregulate CD70 by inducing CD70 promoter hypomethylation.[10,23]

We hypothesize that targeting both the proliferative and the stem cell compartment of the pool of AML blasts with cusatuzumab, in combination with the upregulation of CD70 with azacitidine, may result in better clinical outcomes for patients with AML. It is anticipated that azacitidine's effectiveness will be enhanced by the antiproliferative and stemness-reducing activity of cusatuzumab and that combination therapy will have a complimentary effect on AML. The preliminary efficacy of cusatuzumab and azacitidine combination therapy was demonstrated in study ARGX-110-1601. Additionally, the safety profiles of the agents indicate that toxicities are not overlapping and adverse events will be managed with monitoring and supportive care (Section 2.2.2).

2.1.4. Rationale for Dose Selection

Preclinical and clinical data analyzed to date suggest that a target steady-state trough concentration (C_{trough}) of cusatuzumab >100 µg/mL (bone marrow concentration >20 µg/mL) is required for both bone marrow penetration and to elicit strong clinical responses in the heterogenous AML population. Based on preliminary clinical pharmacokinetic modeling and simulation, the median serum cusatuzumab C_{trough} >100 µg/mL at steady-state should be achieved after 5 to 6 doses (ie, 2-3 cycles) at dose levels of 10 mg/kg (median predicted C_{trough} ~103 µg/mL) or by the second dose (ie, 1 cycle) at 20 mg/kg (median predicted C_{trough} ~208 µg/mL) given every 2 weeks. Analysis from Study ARGX-110-1601 suggests that these dosages are advantageous because the negative impact of anti-drug antibodies (ADAs) on serum cusatuzumab exposure was more apparent at lower doses (ie, 1 and 3 mg/kg) compared with higher doses (ie, 10 and 20 mg/kg). Specifically, ADA-positive subjects treated at the lower doses showed lower serum cusatuzumab exposure compared with ADA-negative subjects. Doses of cusatuzumab below 10 mg/kg were subtherapeutic with a higher incidence of ADAs; thus, they were not considered for further exploration.

Additionally, efficacy results from Study ARGX-110-1601 support further exploration of doses of cusatuzumab ≥10 mg/kg administered every 2 weeks. The dose-escalation Phase 1 portion of the study had a CR rate of 67% overall (n=8/12) and in each of the studied dose levels (2 of 3 subjects in each of the following doses: 1, 3, 10, and 20 mg/kg). Notably, both subjects in the 20 mg/kg dose who achieved CR had adverse-risk AML by cytogenetics and molecular profiling; moreover, neither had disease progression after at least 60 weeks of therapy. Contrary to this observation,

none of the subjects at 10 mg/kg dose level had adverse cytogenetics in Part 1; however, all have progressed with longer follow-up.

The safety profile of cusatuzumab at all dose levels remains favorable, with only IRRs being reported above the expected azacitidine toxicities. There appears to be no relevant differences in safety profiles across the dose levels tested or among subjects.

Based on the safety, efficacy, and PK assessments of cusatuzumab in ARGX-110-1601 study (Section 2.2.2.1), doses of cusatuzumab ≥10 mg/kg given Q2W may be required to achieve optimal therapeutic levels in the bone marrow and may also provide target exposure across a larger spectrum of patients due to observed high inter-subject variability and heterogeneity of AML population and disease burden.

The dose of azacitidine used in this study (75 mg/m^2 BSA) is as indicated in the azacitidine Summary of Product Characteristics (SPC) and the United States Package Insert (USPI).

2.1.5. Rationale for Administration Schedule

Preliminary Cycle 1 data from study ARGX-110-1201 showed dose proportionality over the dose range studied, and a half-life ($t_{1/2}$) of approximately 11 days. Therefore, a 2-week dosing schedule was chosen for this study. In study ARGX-110-1601 a monotherapy dose of cusatuzumab was given 2 weeks prior to initiation of cusatuzumab plus azacitidine combination therapy in order to collect safety, PK, PD, and efficacy data regarding cusatuzumab monotherapy in this patient population. For this study, the monotherapy dose has been removed in order to provide standard of care therapy with azacitidine from the onset of study treatment given that sufficient safety, PK, PD, and efficacy data has been collected in ARGX-110-1601. All participants in this study will receive azacitidine on Days 1 through 7 and cusatuzumab on Day 3 and Day 17 of each 28-day cycle.

2.2. Background

2.2.1. Acute myeloid leukemia

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by uncontrolled clonal expansion of hematopoietic progenitor cells. As the most common form of acute leukemia, AML accounts for the largest number of annual deaths from leukemia. This poor prognosis is in part due to the fact that AML affects patients at a more advanced median age of 67 years with a third of patients diagnosed at an age of over 75 years.[17,18] Advanced age associated with comorbidities, end-organ dysfunction, and poor performance status severely limits tolerance to intensive chemotherapy.

In addition, the biology of AML in the elderly contributes to the poor therapeutic outcome. In older patients, AML arises more frequently from an overt or unrecognized myelodysplastic syndrome (MDS), and appears to be associated with complex, monosomal, or combination karyotypes, adverse cytogenetics, as well as a multidrug resistant phenotype.[15] In recent years, hypomethylating agents such as azacitidine and decitabine have emerged as one of the preferred therapies for AML patients who cannot tolerate intense induction and consolidation

chemotherapy.[4,15] Azacitidine or decitabine monotherapy results in low response rates (10%-50%, including hematologic improvement), requires 3.5 to 4.3 months to achieve best response, and is not curative, with a median overall survival (OS) of less than 1 year.[7,12] Thus, there is a critical need to develop targeted therapies capable of rapidly inducing a high rate of clinical response, with better tolerability and durable responses for elderly patients with AML.

2.2.2. Cusatuzumab

Cusatuzumab is a humanized monoclonal antibody of camelid origin, binding with high affinity to human CD70. Cusatuzumab has been modified using Potelligent® technology to induce enhanced antibody-dependent cell-mediated cytotoxicity (ADCC)[16] for therapeutic use in patients with advanced cancer.

Cusatuzumab is targeted to CD70, a cell surface antigen normally expressed in a small subset of activated B- and T- lymphocytes as well as mature dendritic cells,[2] and is involved in lymphocyte differentiation and survival signaling upon binding to its cell surface receptor, CD27.[1] CD70-induced signaling of CD27 results in increased production and activation of regulatory T cells.[5] Cusatuzumab is a potent and dose-dependent inhibitor of CD27 signaling.

CD70 expression is low or absent from normal tissues of all vital organs. CD70 is over-expressed in several tumor types, including AML, often together with CD27 in hematological malignancies suggesting its involvement in proliferation and survival of the malignant cells.[2,19] Soluble CD27 (sCD27) level, which results from ligation of CD70 to its receptor and subsequent cleavage by a cell surface protease, is elevated in acute lymphoblastic leukemia[19] and other B cell lymphomas and leukemias.[2,26]

CD70 also appears to play a role in evasion of immune surveillance by inducing T cells with regulatory potential thus promoting tumor growth.[5,11,28]

Inhibition of the CD70-CD27 signaling pathway in regulatory T cells is also believed to impede regulatory T cell recruitment or activation thereby potentially restoring a participant's immune-surveillance in the tumor microenvironment.[5] Cusatuzumab also exerts antibody-dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC) of CD70 positive tumor cells.

It is therefore expected that cusatuzumab, by virtue of its pleiotropic mechanisms of action, has increased cell killing properties compared to other CD70 targeting agents, ie, by induction of cytotoxicity against CD70-positive tumor cells via enhanced antibody effector mechanisms, and by blocking proliferation and survival signals of malignant cells and induction of an anti-tumor immune response following interruption of CD70-CD27 signaling.[24]

2.2.2.1. Clinical Data

Cusatuzumab currently is being investigated in 3 studies:

- Study ARGX-110-1201 is a completed Phase 1 study in adult subjects with advanced malignancies expressing CD70. Subjects received cusatuzumab monotherapy by intravenous

(IV) infusions, once every 3 weeks. In the dose escalation part, a total of 26 subjects with solid tumors or hematological malignancies expressing CD70 were treated with cusatuzumab at a dose of 0.1 mg/kg (n=6), 1 mg/kg (n=5), 2 mg/kg (n=7), 5 mg/kg (n=3), or 10 mg/kg (n=5). In the dose expansion part, a total of 73 subjects were treated with cusatuzumab at a dose of 1 mg/kg (n=2) or 5 mg/kg (n= 71).

- Study ARGX-110-1401 is an ongoing Phase 1 safety and feasibility study in subjects with nasopharyngeal carcinoma, who receive treatment with cusatuzumab by IV infusions, once every 3 weeks. As of 30 September 2018, 11 subjects have been treated with 5 mg/kg cusatuzumab.
- Study ARGX-110-1601 is an ongoing Phase 1/2, dose-escalation, safety, and efficacy study in subjects with previously untreated AML or high-risk myelodysplastic syndrome (MDS) who receive treatment with cusatuzumab monotherapy on Day 1 of a 14 day first cycle followed by cusatuzumab IV every 2 weeks on Days 3 and 17 of each 28-day cycle and azacitidine on Days 1 to 7 of each cycle, at the standard dose of 75 mg/m^2 subcutaneous injection. As of 30 September 2018, 20 subjects have been treated with cusatuzumab; 3 subjects each at doses of 1, 3, 10, and 20 mg/kg in the dose escalation portion of the study and 8 additional subjects were treated at 10 mg/kg following selection of this dose for further evaluation.

At the cut-off date of 30 September 2018, cusatuzumab has been administered to 130 subjects. Please see the Investigator's Brochure for further details.

Safety

The most commonly reported drug-related treatment-emergent adverse events (TEAEs) were fatigue, infusion-related reactions (IRRs), pyrexia, dyspnea, decreased appetite, abdominal pain, nausea, and anemia. The majority of these events were National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 1 or Grade 2 with no significant differences between dose levels, including 10mg/kg and 20mg/kg.

Apart from IRRs, which were manageable with concomitant medication, the frequency and profile of reported adverse events in all cusatuzumab studies is consistent with the symptomology of the underlying disease.

As of 15 October 2018, in the Phase 1 portion (n=12) of the ARGX-110-1601 study of cusatuzumab in combination with azacitidine in AML patients, other than expected IRRs, there were no safety signals identified other than known azacitidine toxicities. Infusion-related reactions were generally low grade; 1 subject (7.1%) was reported with a Grade 3 IRR leading to cusatuzumab discontinuation. Fifty percent of subjects (6 of 12) were reported with Grade 3 or 4 hematologic toxicities including anemia, thrombocytopenia, neutropenia, leukopenia and febrile neutropenia.

Efficacy

As of 15 October 2018, in the Phase 1 portion of the ARGX-110-1601 study (n=12), 50% of subjects had adverse risk AML and the median age was 75 years. Eight subjects (67%) achieved CR and 11 subjects (92%) demonstrated a response including CR, CRi, and partial response (PR) and 1 subject (8.3%) had stable disease. The median time to first response was 14 weeks and 3 subjects (25%) reached a first response after a single dose of cusatuzumab (prior to initiation of azacitidine therapy). The median duration of response was 5.5 months. The median event free survival was 8.1 months (range: 2 months - 17.4 months).

Pharmacokinetics

In the Phase 1 portion of study ARGX-110-1601, four dose levels (1, 3, 10 and 20 mg/kg every 2 weeks) of cusatuzumab in combination with azacitidine were administered to AML patients. Based on preliminary PK analysis, for dosing regimens of 1 and 3 mg/kg every 2 weeks, the serum drug exposures were lower after the 2nd dose compared to that of the 1st dose due to the presence of ADA. Doses of 1 or 3 mg/kg every 2 weeks resulted in peripheral C_{trough} of <50 µg/mL in AML patients. A linear PK was observed in the dose range of 10 to 20 mg/kg administered every 2 weeks with an estimated mean half-life of 200 to 262 hr (8.3-11 days). A peripheral C_{trough} >100 µg/mL was achieved with dosing regimens of 10 mg/kg and 20 mg/kg every 2 weeks for subjects with adverse risk AML.

In study ARGX-110-1201, cusatuzumab demonstrated dose proportionality over the dose range of 1 to 10 mg/kg, but not at 0.1 mg/kg. The median maximum concentration (C_{max}) in Cycle 1 was 1.6 µg/mL, 21.6 µg/mL, 39.4 µg/mL, 109.0 µg/mL and 287.0 µg/mL, and the median area under the curve (AUC) was 4072.2, 9036.6, 35845.1 and 72437.8 µg×h/mL for the 1, 2, 5, and 10 mg/kg cohorts, respectively. The median $t_{1/2}$ of cusatuzumab ranged from 263.1 hours for the 1 mg/kg cohort to 315.3 hours for the 10 mg/kg cohort (11 to 13.1 days). The data should be carefully interpreted because of the limited number of subjects and short observation window. There were no apparent correlations between PK parameters and either clinical treatment response or adverse events (AEs).

Immunogenicity

In the Phase 1 portion of ARGX-110-1601 study of cusatuzumab in combination with azacitidine in AML patients, based on preliminary analysis, no ADA was observed in 3 of 3 subjects treated with 20 mg/kg cusatuzumab every 2 weeks and 1 of 3 subjects were ADA positive who were treated with 10 mg/kg cusatuzumab every 2 weeks. However, the presence of ADA has minimum impact on the drug exposure achieved at high doses (≥10 mg/kg). At the dose level of 1 mg/kg every 2 weeks, 3 of 3 subjects were ADA positive and at the dose level of 3 mg/kg every 2 weeks, 2 of 3 subjects were ADA positive and presence of ADA resulted in faster clearance and relatively lower exposure.

In the dose escalation of the Phase I study ARGX-110-1201, anti-drug antibodies (ADAs) appeared to be inversely related to the administered dose. Following administration of the first dose of cusatuzumab, ADA responses were observed in all subjects in the 0.1 mg/kg cohort, 60.0%

of subjects treated in the 1 mg/kg cohort, 42.9% of subjects treated in the 2 mg/kg cohort and 33.3% of subjects treated in the 5 mg/kg cohort. No subjects in the 10 mg/kg cohort had positive ADA results following administration of the first dose of cusatuzumab.

For the subjects at the lowest dose group (0.1 mg/kg), PK data suggest that ADAs are associated with an accelerated clearance of cusatuzumab. At doses of 1 mg/kg and above where only low ADA titers were observed, significantly accelerated clearance of cusatuzumab has not been observed.

In the safety extension phase, in which subjects received 5 mg/kg cusatuzumab, ADAs were observed in 1 of 15 subjects with hematological malignancies; no subjects with solid tumors had ADAs. For the most comprehensive nonclinical and clinical information regarding cusatuzumab, refer to the latest version of the cusatuzumab Investigator's Brochure.

2.2.3. Azacitidine

Azacitidine (5-azacytidine) is a pyrimidine nucleoside analogue of cytidine with antineoplastic activity. Azacitidine is indicated for the treatment of adult patients with AML or intermediate 2 and high-risk MDS with >20% marrow blasts who are not eligible for hematopoietic stem cell transplantation. The most common side effects with azacitidine in patients with MDS, chronic myelomonocytic leukemia (CMML) or AML, which were seen in more than 60% of patients, are thrombocytopenia, neutropenia, leucopenia, nausea and vomiting, and injection site reactions. For the most up to date information refer to the azacitidine Summary of Product Characteristics (SPC) and USPI.

2.3. Benefit/Risk Assessment

Cusatuzumab is a first-in-class anti CD70 ADCC-enhanced antibody that selectively targets LSCs and blast cells of AML patients while sparing normal hematopoietic stem cells that lack CD70 expression. Additionally, preclinical data demonstrated that treatment with azacitidine upregulates CD70 on AML LSCs, suggesting that treatment with combination therapy of cusatuzumab and azacitidine may have a synergistic inhibitory effect on AML growth.

Patients with AML who are generally older and are not candidates for intensive chemotherapy are known to have poor outcomes. The proposed combination of cusatuzumab with azacitidine, a hypomethylating agent (HMA), ensures standard-of-care for patients who cannot benefit from other currently available intensive chemotherapy options, and may lead to a potent, synergistic therapeutic effect, resulting from the different underlying mechanisms of action by the 2 agents.

Results from the ongoing clinical studies show that the risks with cusatuzumab appear to be mainly limited to infusion-related reactions (IRRs), a recognized adverse reaction associated with the administration of antibodies.[14] In the current study, that risk will be managed with the use of a prophylactic premedication regimen consisting of anti-pyretics, anti-histamines, and corticosteroids (see Section 6.1.1).

Additionally, study ARGX-110-1601 demonstrated a safety profile similar to that of azacitidine with the addition of IRRs in an untreated AML patient population and demonstrated efficacy with

an overall response rate of 92% and CR rate of 67%. Taken together, the administration of cusatuzumab in combination with standard doses of azacitidine in patients with newly diagnosed AML who are not fit for intensive chemotherapy (ie, generally older or with comorbidities) is considered to have a manageable safety profile. The safety profiles of the 2 agents indicate that toxicities are non-overlapping and adverse events can be managed with monitoring and supportive care. More detailed information about the known and expected benefits and risks of cusatuzumab is provided in the IB.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To determine the efficacy of cusatuzumab in combination with azacitidine in patients with previously untreated AML who are not eligible for intensive chemotherapy	Complete response (CR) rate per ELN 2017 (Dohner 2017)[6]
Secondary	
To determine other response measures (see definitions in Table 6)	• Rate of CRh • Rate of CR + CRh • Rate of CRi • Overall response rate (ORR) = Rate of CR+ CRh+ CRi • Rate of CR without MRD • Rate of MRD negativity among participants achieving CR, CRh, CRi, or MLFS; defined as less than 1 blast or leukemic stem cell in 1,000 leukocytes (MRD level $<10^{-3}$)
To assess time to response and duration of response	Time to response, defined as time from randomization in Part 1 or enrollment in Part 2 to achieving the first response of CR, CRh, or CRi; duration of response, defined as time from achieving the first response of CR, CRh, or CRi to disease relapse or death from any cause.
To determine transfusion independence	Transfusion independence (RBC or platelets) is defined as a period of at least 56 consecutive days with no transfusion between first dose of study drug and the last dose of study drug + 30 days.
To assess the safety profile of cusatuzumab in combination with azacitidine	Safety profile of Adverse Events (AE) and Serious Adverse Events (SAE)
To assess the pharmacokinetics of cusatuzumab alone and in combination with azacitidine	Pharmacokinetics

Objectives	Endpoints
To assess the immunogenicity of cusatuzumab alone and in combination with azacitidine	Immunogenicity / anti-drug antibody testing
Exploratory	
To assess progression-free survival (PFS)	PFS is defined as the time from randomization in Part 1 or enrollment in Part 2 to progressive disease, relapse from CR/CRh/CRi, or death from any cause, whichever occurs first.
To assess overall survival (OS)	OS is defined as the time from randomization in Part 1 or enrollment in Part 2 to death
To assess pharmacodynamics and to explore biomarkers predictive of clinical response	Exploratory biomarkers including baseline level of CD70+ blasts, CD70+LSC, sCD27, NK cells
To assess patient-reported symptom severity and health-related quality of life	PROs using the FACT-Leu and EQ 5D 5L (See Section 10.8 Appendix 8 and Section 10.9 Appendix 9)
To collect medical resource utilization (MRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this study).	Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit) Outpatient medical encounters and treatments (including physician or emergency room visits, selected tests and procedures, and medications)

HYPOTHESIS

The primary hypothesis of this study is that the combination of cusatuzumab at doses of 10 mg/kg or 20 mg/kg with azacitidine has a CR rate of no less than 35% in patients with previously untreated AML who are not eligible for intensive chemotherapy.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label study. The study will consist of 2 sequential parts, Part 1 and Part 2, as described below. The purpose of Part 1 is to select a dose schedule based on the totality of the data, including CR rate and other efficacy endpoints, PK, biomarkers, and safety. The purpose of Part 2 is to further evaluate and confirm the efficacy and safety of the combination therapy at the selected dose of cusatuzumab.

NOTE: Part 2 of the study will not be conducted because further development of this regimen (cusatuzumab in combination with azacitidine) in patients with unfit AML will not be pursued due to the evolving treatment landscape in AML.

NOTE: After 22 Oct 2021, ongoing subjects (on treatment or in follow-up) will be treated and assessed according to a reduced schedule of assessment (Table 1A).

Part 1 of the study is a randomized study of 2 doses of cusatuzumab in combination with azacitidine in patients with previously untreated AML who are not eligible for intensive chemotherapy. Part 2 of the study is an expansion of the selected dose. The study will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 28 days prior to randomization. The Treatment Phase will extend from Cycle 1/ Day 1 until study intervention discontinuation. Participants will be treated with their assigned dosing regimen until disease progression, relapse, unacceptable toxicity, or withdrawal due to investigator discretion or withdrawal of consent. The Follow-up Phase will begin once a participant discontinues study intervention, and will continue until death, loss to follow up, consent withdrawal for study participation, or study end, whichever occurs first. Safety and efficacy data will be closely monitored on an ongoing basis by the Sponsor's central clinical team.

Part 1:

During Part 1, participants will be stratified by type of AML (de novo versus secondary AML) and ECOG score (0-1 versus 2) and then assigned randomly in a 1:1 ratio to receive cusatuzumab and azacitidine according to 1 of the following 2 dosing regimen groups:

- Group A: Azacitidine 75 mg/m^2 SC or IV on Day 1 through Day 7, cusatuzumab 10 mg/kg IV on Day 3 and Day 17 of each 28-day cycle
- Group B: Azacitidine 75 mg/m^2 SC or IV on Day 1 through Day 7, cusatuzumab 20 mg/kg IV on Day 3 and Day 17 of each 28-day cycle

Part 1 of the study utilizes a 3-stage monitoring approach as the statistical guidance to select a dose schedule (see Section 9.5, Interim Analysis). The cumulative number of participants for each dose group at each of the 3 stages are 15, 30, and 50, respectively. Response will be based on all evaluations up to the time point when the last participant is treated for a minimum of 3 cycles with combination therapy (cusatuzumab + azacitidine). At each stage, available data of efficacy, safety, pharmacodynamics, and biomarkers will be evaluated by a Data Review Committee (DRC) to determine if either or both of these treatment groups should continue into the next stage of Part 1, and by the end of Part 1 (n=50/group), to select 1 dose schedule to be continued into study Part 2. The DRC will be formed prior to the first participant being enrolled in the trial and will remain in place until the conclusion of the trial. Enrollment does not pause at each stage. Refer to Committees Structure in Appendix 3 (Section 10.3), Regulatory, Ethical, and Study Oversight Considerations for details.

If, based upon the totality of the data, 1 treatment group is considered to be less effective at any stage of Part 1, then that treatment group will be closed to enrollment. Upon 1 dose level being selected to continue, the DRC may determine to switch ongoing participants to treatment with the dose level selected. If 1 dose group is determined at Stage 1 or Stage 2 not to continue, the other dose group will be continued into study Part 2 directly without further evaluations in Part 1. Enrollment will continue at each of the above 3 stages while efficacy and safety data are accumulated and evaluated.

Additionally, after 5, 15, 30, and 50 participants have enrolled on each arm, respectively, and been treated for 3 cycles, cumulative safety data will be evaluated by the DRC to ensure continued study treatment is safe.

Part 2:

For Part 2, the treatment group to be studied will be dependent upon the results from Part 1. At the end of Part 1, all available data will be evaluated by the DRC to select 1 of the cusatuzumab treatment groups for further evaluation in Part 2.

The sample size for Part 2 will result in approximately 100 participants for the selected treatment group from Parts 1 and 2 combined. A formal interim analysis of the primary endpoint, CR rate, is planned during Part 2 to include 80 participants from the selected dose group, at the time when the last participant of the 80 has been treated for a minimum of 4 cycles of combination therapy. The final analysis will be based on 100 participants. A diagram of the study design is provided in Section 1.2, Figure 1.

NOTE: Part 2 of the study will not be conducted because further development of this regimen (cusatuzumab in combination with azacitidine) in patients with unfit AML will not be pursued due to the evolving treatment landscape in AML.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

Randomization will be used to allocate participants to the 2 dose schedule groups in study Part 1. Although there is no formal statistical comparison between the 2 groups, randomization can minimize bias and imbalance in baseline characteristics between the 2 dose groups to facilitate the decision making of selecting a dose schedule.

This is an open-label study.

DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, safety, or tolerability of cusatuzumab and azacitidine and to identify genetic factors associated with AML.

Biomarker samples will be collected to evaluate the mechanism of action of cusatuzumab and azacitidine or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The goal of the biomarker

analyses is to evaluate the PD of cusatuzumab and azacitidine and aid in evaluating the intervention-clinical response relationship.

DNA and Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

Patient-Reported Outcomes

Patient-reported outcomes will be collected to monitor participants' symptoms and health-related quality of life. PRO data will be used to describe any changes in symptoms and/or HRQoL over the course of treatment. Direct patient reports may also provide supplemental information about dose tolerability.

Medical Resource Utilization

Medical resource utilization (MRU) data will be collected to determine the medical cost impact of the treatment regimen. The data collected will be used to conduct exploratory analyses that may be used to support the value and cost-effectiveness modeling for market access.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

Study ARGX-110-1601 demonstrated similar safety and efficacy in subjects with AML treated with cusatuzumab at 10 mg/kg and 20 mg/kg every two weeks in combination with azacitidine. Participants on this study, CULM20236, will be treated with 1 of these 2 dose levels that have already shown promising preliminary response results. Additionally, all participants on this study receive standard of care treatment for their disease with azacitidine which has shown to be effective in this patient population and has a manageable safety profile. The clinical equipoise between the two dose levels and receipt of standard of care, along with the risk benefit considerations discussed earlier, attest to an ethical study design. Safety and efficacy data for all participants will be closely and frequently monitored to ensure the risk benefit ratio favors continued treatment.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross (see Section 8.1).

4.3. Justification of Dose

The selection of doses for cusatuzumab and azacitidine are discussed in Section 2.1.4 Rationale for Dose Selection.

4.4. End of Study Definition

The end of study will be reached when all subjects have completed or discontinued study treatment. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final participant visit at the study site, in the time frame specified in the Clinical Trial Agreement.

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days of randomization unless otherwise noted in the Schedule of Activities. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate Sponsor representative and resolve any issues before enrolling a participant in the study. The Sponsor will review patient eligibility before participants are enrolled. Waivers are not allowed.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. ≥18 years of age

2. Criterion modified per Amendment 1

2.1 AML according to WHO 2016 criteria and fulfilling all of the following criteria that defines those who are "not candidates for intensive chemotherapy":

- ≥75 years of age or
- <75 years of age with of at least one of the following comorbidities:
  - ECOG Performance Status of 2
  - Severe cardiac comorbidity defined as congestive heart failure or ejection fraction ≤50%
  - Severe pulmonary comorbidity defined as documented pulmonary disease with lung diffusing capacity for carbon monoxide (DLCO) ≤65% of expected, or forced expiratory volume in 1 second (FEV_1) ≤65% of expected or dyspnea at rest requiring oxygen
  - Moderate hepatic impairment defined according to NCI organ dysfunction classification criteria (total bilirubin ≥1.5 up to 3 times upper limit of normal [ULN])
  - Creatinine clearance <45 mL/ min/1.73 m² (by MDRD formula)
  - Comorbidity that, in the Investigator's opinion, makes the patient unsuitable for intensive chemotherapy and must be documented and approved by the Sponsor before randomization

3. Criterion numbering modified per Amendment 1

3.1 De novo or secondary AML.

4. Criterion modified per Amendment 1

4.1 Previously untreated AML (except: emergency leukapheresis, hydroxyurea, and/or 1 dose of cytarabine [eg, 1-2g/m^2] during the Screening Phase to control hyperleukocytosis. These treatments must be discontinued ≥24 hours prior to start of study drug). Empiric all trans retinoic acid (ATRA) treatment for presumed acute promyelocytic leukemia (APL) is permitted but APL must be ruled out and ATRA must be discontinued ≥24 hours prior to the start of study drug;

5. Criterion numbering modified per Amendment 1

5.1 Not eligible for an allogeneic hematopoietic stem cell transplantation.

6. Criterion numbering modified per Amendment 1

6.1 ECOG Performance Status score of 0, 1 or 2.

7. Criterion numbering modified per Amendment 1

7.1 The following clinical laboratory values at screening:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <3 times ULN; for participants with leukemic infiltration of the liver (documented by biopsy or imaging), AST and ALT <5 times ULN is permitted
- Total bilirubin ≤ 3 times ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin or in case of liver infiltration by AML (documented by biopsy or imaging) serum total bilirubin <5 times ULN
- Creatinine Clearance >30 mL/min (by MDRD formula)

8. Criterion modified per Amendment 1

8.1 A woman must be either:

- Not of childbearing potential: postmenopausal (amenorrhea for at least 12 months);
- Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for participants in the clinical study while receiving study treatment and for at least 3 months after the last dose of study treatment: Examples of highly effective methods of contraception are located in Appendix 5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information.

  A woman of childbearing potential must have a negative highly-sensitive serum (β-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at screening.

  A woman of childbearing potential must agree to not donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study treatment and for 3 months after the last dose of study treatment.

Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) a woman must begin a highly effective method of birth control, as described above.

9. Criterion modified per Amendment 1

9.1 A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository for at least 3 months after last study treatment.

- Must agree to not donate sperm during the study treatment and for 3 months after the last dose of study treatment.
- Not plan to father a child during the study treatment and for 3 months after the last dose of study treatment.

10. Criterion modified per Amendment 1

10.1. Must sign an informed consent form (ICF) indicating that he or she (or their legally acceptable representative) understands the purpose of, and procedures required for, the study and is willing to participate in the study.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Criterion modified per Amendment 1

1.1 Acute promyelocytic leukemia.

2. Leukemic involvement or clinical symptoms of leukemic involvement of the central nervous system.

3. Criterion modified per Amendment 1

3.1 Use of immune suppressive agents for the past 4 weeks before the first administration of cusatuzumab on Cycle 1 Day 3. For regular use of systemic corticosteroids, participants may only be included if free of systemic corticosteroids for a minimum of 5 days before the first administration of cusatuzumab. Treatment of adrenal insufficiency with physiologic replacement doses of corticosteroids are allowed.

4. Prior treatment with a hypomethylating agent for treatment of AML or MDS

5. Criterion modified per Amendment 1

5.1 Active malignancies (ie, progressing or requiring treatment in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

- Non-melanoma skin cancer treated within the last 24 months that is considered completely cured

- Adequately treated breast lobular carcinoma in situ and breast ductal carcinoma in situ
- Adequately treated cervical carcinoma in situ without evidence of disease
- History of localized breast cancer and receiving antihormonal agents, or history of localized prostate cancer (N0M0) and receiving androgen deprivation therapy
- Malignancy that is considered cured with minimal risk of recurrence

6. Criterion modified per Amendment 1

6.1 Any active systemic infection

7. Criterion modified per Amendment 1

7.1 A history of human immunodeficiency virus (HIV) antibody positive or tests positive for HIV at screening

8. Criterion modified per Amendment 1

8.1 Active hepatitis B or C infection or other clinically active liver disease

Seropositive for hepatitis B: defined by a positive test for hepatitis B surface antigen [HBsAg]. Participants with resolved infection (ie, participants who are HBsAg negative with antibodies to total hepatitis B core antigen [anti-HBc] with or without the presence of hepatitis B surface antibody [anti-HBs]) must be screened using real-time polymerase chain reaction (RT-PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are RT-PCR positive will be excluded. Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by RT-PCR.

Known Hepatitis C infection or positive serologic testing for Hepatitis C (anti-HCV antibody)

9. New York Heart Association Class IV heart failure or ongoing unstable angina (See Section 10.7 Appendix 7)

10. Known allergies, hypersensitivity, or intolerance to cusatuzumab or azacitidine or its excipients (ie, mannitol, an excipient of azacitidine).

11. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or physical limitations that could prevent, limit, or confound the protocol-specified assessments.

12. Criterion modified per Amendment 1

12.1 Major surgery (eg, requiring general anesthesia) within 4 weeks prior to initiation of the study.

13. Criterion added per Amendment 1
Women who are breastfeeding

14. Criterion added per Amendment 1
Received a live, attenuated vaccine within 4 weeks prior to initiation of study treatment.

NOTE: Investigators should ensure that all study enrollment (inclusion/exclusion) criteria have been met at screening and prior to the first dose of study intervention. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3 (Section 10.3) Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

- Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (eg, contraceptive requirements).
- Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.
- In addition to contraceptive precautions discussed for male participants in Inclusion Criterion 9 and Appendix 5, male participants should inform fertile female partners to use effective methods of birth control.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the Sponsor study-site contact for completeness.

The participant identification and randomization log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once after prior discussion with the Sponsor clinical team.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

In this protocol, "study intervention" refers to treatment with cusatuzumab or azacitidine. Detailed information on the composition of the study interventions can be found in the Investigator's Brochure for cusatuzumab, and in the azacitidine label.

Study intervention administration must be captured in the source documents and the eCRF. Study interventions may be dispensed only by the investigator or by a member of study staff specifically authorized by the investigator, as appropriate.

Dosing schedule

After randomization, participants will receive combination therapy in 28-day cycles beginning with Cycle 1 Day 1, with azacitidine administered SC or IV (per local standard of care) at the standard dose of 75 mg/m² BSA on Days 1 through 7 of each cycle and cusatuzumab administered IV on Days 3 and 17 of each cycle. If Day 1 of azacitidine must be administered before Day 28 of the prior cycle due to scheduling or logistical reasons, a +/- 2 day window is allowed for the start of a cycle. The dose of the cusatuzumab will be based on the treatment group to which the participant is randomized, as follows:

- Treatment Group A: Azacitidine 75 mg/m^2 SC or IV on Day 1 through Day 7; cusatuzumab 10 mg/kg IV on Day 3 and Day 17 of each 28-day cycle
- Treatment Group B: Azacitidine 75 mg/m^2 SC or IV on Day 1 through Day 7; cusatuzumab 20 mg/kg IV on Day 3 and Day 17 of each 28-day cycle

Body surface area and dose should only be recalculated if there is >10% weight change from the weight used in the previous dose calculation.

The infusion of cusatuzumab will be started at a rate of 10 mL/hour. In the absence of IRRs, the infusion rate may be doubled every 30 minutes, to a maximum of 160 mL/hour. Cusatuzumab administration is according to the schedule given in the Pharmacy Manual and according to the tolerability of the intervention by the participant. In the absence of IRRs, subsequent infusions may be administered at the highest rate that was well tolerated in the preceding infusion. Refer to IRR guidelines in Section 6.6.1.

When cusatuzumab and azacitidine are scheduled to be administered on the same day, azacitidine should be administered first. It is recommended that there is at least a 30-minute waiting time between the end of azacitidine administration and the start of the cusatuzumab infusion.

6.1.1. Premedications

Pre-medication will be administered prior to each cusatuzumab infusion as follows. Variance based on institutional practice is acceptable once discussed with the Sponsor.

- Acetaminophen (eg, 650-1000 mg PO) approximately 30 minutes prior to the planned infusion time
- Antihistamine (eg, diphenhydramine 25-50 mg or equivalent antihistamine) PO or IV; approximately 30 minutes prior to the planned infusion time
- Corticosteroids (eg, methylprednisolone 125 mg or dexamethasone 20 mg); IV approximately 1-3 hours prior to the planned infusion time

For participants who do not experience IRRs for the first three cusatuzumab infusions, subsequent doses of cusatuzumab may be administered with only acetaminophen and antihistamine as pre-medication with no corticosteroids, or lower doses of corticosteroids if deemed necessary.

Participants should be premedicated with anti-emetics for nausea and vomiting according to standard practice and as indicated in the azacitidine SPC and USPI.

6.1.2. Anti-infective Prophylaxis

Anti-infective prophylaxis (antibacterial, antifungal, or antiviral) on study should primarily be guided by institutional drug-resistance patterns and prevalent organisms. For participants in this study prophylaxis with a quinolone should be given at the start of therapy per ELN recommmendations.[6] During periods of severe neutropenia (defined as ANC<500), prophylaxis with an antiviral agent such as acyclovir or valacyclovir and antifungal agent such as posaconazole, voriconazole, fluconazole must be initiated. Pneumocystis prophylaxis should also be considered.

6.2. Preparation/Handling/Storage/Accountability

Study Intervention Information - Cusatuzumab

Cusatuzumab must be stored according to the label.

Body weight used for cusatuzumab dose calculation is capped at a maximum of 100 kg (please refer to the Pharmacy manual for more details). Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

Study Intervention Information – Azacitidine

Azacitidine must be stored as indicated on the clinical label.

Refer to the pharmacy manual and SPC or USPI for additional guidance on study intervention preparation, handling, and storage.

6.3. Measures to Minimize Bias: Randomization and Blinding

Participants will be randomized to 1 of the 2 dosing groups. Randomization will be stratified by type of AML (de novo versus secondary) and ECOG score (0-1 versus 2).

Blinding

As this is an open-label study, blinding procedures are not applicable.

6.4. Study Intervention Compliance

Cusatuzumab will be administered as an IV infusion by qualified staff; azacitidine will be administered by subcutaneous injection or IV infusion by qualified staff. The details of each administration will be recorded in the eCRF and the participant's medical records.

6.5. Concomitant Therapy

Prestudy therapies administered up to 28 days before first dose of study intervention must be recorded at screening. Prior systemic therapies for MDS or myeloproliferative neoplasms (MPN) administered before signing of the informed consent should be collected at screening.

Concomitant therapies must also be recorded through the study beginning with the start of the first dose of azacitidine to 30 days after the last dose of study intervention. All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) different from the study intervention must be recorded in the eCRF. Recorded information will include description of the type of therapy, start and stop date, duration of use, dosing regimen, route of administration, and indication.

6.5.1. Permitted Therapies

All concomitant medications for medical conditions other than AML are permitted, as clinically indicated. Localized or hormonal treatment for non-AML malignancies and localized radiotherapy for conditions other than AML may be considered with approval of the Sponsor. All supportive therapies, needed for the management of participants enrolled in this study, are permitted, except for those listed as prohibited therapies.

The following medications and supportive therapies are examples of supportive care therapies that are recommended during the study:

- Short-term (≤7 days) treatment with low doses of systemic corticosteroids when medically necessary for the control of acute symptoms or as premedication for cusatuzumab; topical corticosteroids are permitted
- Prophylactic antibacterial, antifungal, or antiviral agents per ELN guidelines (see Section 6.1.2);
- Growth factors should be used for the treatment of febrile neutropenia (temperature ≥38.5°C and absolute neutrophil count < 1,000/μL) or an active bacterial or fungal infection (ie, requiring intravenous anti-infectives or extensive supportive care) in neutropenic participants. Growth factors need to also be used to prevent treatment delay due to neutropenia.

- Red blood cell and platelet transfusions per institutional guidelines.

6.5.2. Prohibited Therapies and Procedures

The following medications are prohibited during the study treatment:

- Leukapheresis or other concurrent non-study anticancer therapy;
- Any additional monoclonal antibody;
- Investigational agents; and
- Live attenuated vaccination.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.5.3. Subsequent Anticancer Therapy

Data on subsequent anticancer therapy (AML directed therapy, radiotherapy, surgery, or hematopoietic stem cell transplant) administered after the last dose of study intervention should be documented in the eCRF (including start and end date and best response, if available) until the clinical cutoff for the primary CSR analysis.

6.6. Dose Modification

Participants will be treated with their assigned dosing regimen until disease progression, relapse, unacceptable toxicity, or withdrawal due to investigator discretion or withdrawal of consent.

6.6.1. Management Guidelines for Potential Toxicities During Cusatuzumab Infusion

Trained study staff at the study site should be prepared to intervene in case any IRRs occur. Resuscitation equipment and other agents necessary to treat anaphylaxis must be readily available (eg, epinephrine, corticosteroids, IV anti-histamines, bronchodilators, and oxygen). Attention to staffing should be considered when multiple participants will be dosed at the same time. Participants should be monitored for IRRs for 1 hour after completion of the cusatuzumab infusion. If after 3 cycles no IRRs are seen, monitoring after the infusion can be discontinued.

For IRRs and hypersensitivity reactions of any grade/severity during the time of cusatuzumab infusion, immediately interrupt the infusion and manage symptoms. Management of IRRs and hypersensitivity reactions may require reduction in the rate of infusion for future treatment cycles. The following guidance is provided for investigators.

- Grade 1-2 (mild to moderate) IRRs or hypersensitivity reactions: Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the participant does not experience any further reaction symptoms, infusion rate escalation may resume incrementally.
- Grade 3 (severe) IRR or hypersensitivity reaction: Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the participant does not experience additional symptoms the infusion rate may be increased at the

investigator's discretion. Permanently discontinue cusatuzumab upon the third occurrence of a Grade 3 IRR or hypersensitivity reaction.

- Grade 4 (life threatening) IRR or hypersensitivity reactions: permanently discontinue cusatuzumab treatment

Best supportive care should be administered, as applicable. Dose modifications due to toxicity are further described in Section 6.6.2.

Participants should be managed for potential toxicities to azacitidine as indicated in the azacitidine SPC and USPI and Section 6.6.3.

6.6.2. Management Guidelines for Toxicities Attributed to Cusatuzumab

Toxicities attributed to cusatuzumab should be managed by modifying the infusion rate in the case of infusion-related reactions, temporarily stopping cusatuzumab, or discontinuing cusatuzumab altogether. Doses may be postponed based on the severity of and recovery from a previous toxicity. Dose reductions or escalations are not allowed except as recommended by the DRC at the time of dose selection.

The following rules apply with respect to dose delays.

- There should be a time interval of at least 14 days and no more than 35 days between 2 consecutive cusatuzumab doses. If greater than 35 days, investigators should contact the Sponsor's clinical team to determine if the participant can continue to receive cusatuzumab.
- In case the start of a planned treatment cycle is delayed, for example due to recovery from hematological toxicities or logistical/organizational reasons, the subsequent treatment cycle will be the first day of azacitidine administration (Day 1). The administration of cusatuzumab will be shifted according to the shift in azacitidine dosing and will occur on Day 3 and Day 17 of the 28-day azacitidine cycle.
- For participants who develop Grade 4 hematological or Grade 3 to 4 non-hematological toxicities that may be attributed to cusatuzumab alone, cusatuzumab treatment should be postponed until resolution of the adverse event to baseline or ≤ Grade 2. Azacitidine treatment may be maintained during the cusatuzumab interruption within the same cycle. Upon toxicity resolution, cusatuzumab administration should be again aligned with the azacitidine dosing cycle (ie, Day 3 and Day 17 of the 28-day azacitidine cycle).
- A cycle may be delayed (ie, cessation of both study interventions) for up to 21 days from the expected start date of the scheduled cycle; a hold >21 days must be reviewed and approved by the Sponsor's clinical team prior to implementation.

6.6.3. Management Guidelines for Toxicities Attributed to Azacitidine

For participants who develop hematological or non-hematological toxicities that may be attributed to azacitidine alone, azacitidine treatment should be delayed/modified as per azacitidine SPC, USPI, or local standard of care. Cusatuzumab treatment may be maintained on a bi-weekly dosing schedule within the same cycle

The following excerpts describe azacitidine (VIDAZA®) dose reduction guidelines from the VIDAZA SPC.

- Patients without reduced baseline blood counts (ie, White Blood Cells (WBC) ≥3.0 x 10^9 /L and ANC ≥ 1.5 x 10^9 /L, and platelets ≥ 75.0 x 10^9 /L) prior to the first treatment
- If hematological toxicity is observed following Vidaza treatment, the next cycle of the therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, the dose should be reduced according to the following table. Following dose modifications, the cycle duration should return to 28 days.

Nadir Counts		% Dose in the next cycle, if recovery* is not achieved within 14 days
ANC (x 10^9/L)	Platelets (x 10^9/L)	
≤ 1.0	≤ 50.0	50%
> 1.0	> 50.0	100%

*Recovery = counts ≥ nadir count + (0.5 x [baseline count – nadir count])

- Patients with reduced baseline blood counts (i.e. WBC < 3.0 x 10^9/L or ANC < 1.5 x 10^9/L or platelets< 75.0 x 10^9/L) prior to the first treatment
- Following Vidaza treatment, if the decrease in WBC or ANC or platelets from that prior to treatment is ≤ 50%, or greater than 50% but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment made.

  If the decrease in WBC or ANC or platelets is greater than 50% from that prior to treatment, with no improvement in cell line differentiation, the next cycle of Vidaza therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50%, no dose adjustments should be made. If bone marrow cellularity is ≤ 50%, treatment should be delayed and the dose reduced according to the following table:

Bone marrow cellularity	% Dose in the next cycle if recovery is not achieved within 14 days	
	Recovery * ≤ 21 days	Recovery * > 21 days
15-50 %	100%	50%
< 15%	100%	33%

*Recovery = counts ≥ nadir count + (0.5 x [baseline count – nadir count])

- Azacitidine can be administered to participants with renal impairment without initial dose adjustment. If unexplained reductions in serum bicarbonate levels to <20 mmol/L occur, the dose should be reduced by 50% on the next cycle. If unexplained elevations in serum creatinine or blood urea nitrogen (BUN) to ≥2-fold above baseline values and above ULN occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment cycle.

Following dose modifications, the cycle duration should return to 28 days.

6.7. Intervention After the End of Treatment

Participants will be contacted to determine survival and subsequent therapy every 3 months (±7 days) after the last dose of study intervention, unless the participant has died, is lost to follow-up, or has withdrawn consent. If the information on survival, subsequent therapy and other malignancies is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the participant has died, the date and cause of death will be collected and documented on the eCRF.

Investigators may recontact the participant to obtain long-term follow-up information regarding the participant's safety or survival status as noted in the ICF (refer to Informed Consent in Appendix 3 Section 10.3, Regulatory, Ethical, and Study Oversight Considerations).

Participants who are continuing to derive benefit from treatment with cusatuzumab, azacitidine or both agents as assessed by their investigator at the end of the study may continue to receive these medications.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be permanently discontinued if:

- The participant (or the participant’s legally acceptable representative) withdraws consent to receive study intervention
- The participant experiences unacceptable toxicity (participants may discontinue 1 intervention while continuing treatment with the other intervention);
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study intervention
- The participant experiences disease progression or relapse (see Table 6).

If the participant becomes pregnant Refer to Appendix 5 Section 10.5, Contraceptive Guidance and Collection of Pregnancy Information. Treatment should be suspended and the Sponsor’s clinical team should be contacted as soon as possible to discuss study treatment options.

If a participant discontinues study intervention for any reason before the end of the study then the end of treatment assessments should be obtained.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

- The study investigator or Sponsor, for any reason, stops the study or stops the participant's participation in the study

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the Sponsor study site contact of withdrawal of consent for the research samples and to request sample destruction. The Sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the Sponsor that the samples have been destroyed.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 3 Section 10.3 Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedules of Activities summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, biomarker, and safety measurements applicable to this study.

If standard of care tests are performed within the allowable screening period but prior to signing of the ICF the results for these tests may be used for determination of participant eligibility. In this case, after the participant signs the ICF, samples for the local laboratory may not be required, however samples for the central laboratory may still be required as referenced in Schedule of Events.

All PRO assessments should be conducted/completed before any tests, procedures (including bone marrow examination), or other consultations to prevent influencing participant perceptions.

Sample collections for PK and PD assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and the eCRF or lab requisition form.

8.1. Efficacy Assessments

Disease assessments are based on bone marrow evaluations, peripheral blood counts, and the presence of extramedullary disease and will be conducted per the Schedule of Activities at the local laboratory (Table 1/Table 1A). Bone marrow aspirates should be performed for the disease assessment (for bone marrow blasts), for biomarker testing, and for PK. In case of a dry tap, the biopsy may also be utilized for disease assessment. Extramedullary disease evaluations may include computed tomography (CT) scans, magnetic resonance imaging (MRI), positron emission tomography (PET) scans, ultrasound, and physical examinations. See Table 2 for bone marrow biomarker sampling and Table 3 for bone marrow PK sampling. All treatment decisions will be based on local assessments. De-identified copies of the bone marrow aspirate (or biopsy)

pathology report will be sent in to the Sponsor. Transfusion status should also be collected per Schedule of Activities at the time of disease evaluations.

Participants will be assessed for disease status based on the ELN 2017 Response Criteria in AML (Table 6) at the timepoints indicated in Schedule of Activities through CR, CRi, CRh, and at the time of progressive disease. If progressive disease is suspected due to clinical indications or increased peripheral blast counts, then a bone marrow sample must be obtained to confirm progressive disease as defined in Table 6. In the case of overt leukostasis, uncontrollable coagulopathy, or new extramedullary leukemia requiring immediate action and a bone marrow sample cannot be obtained, the Sponsor must be consulted to confirm progressive disease for the participant.

Before participants discontinue the Treatment Phase due to progressive disease or relapse from CR/CRi/CRh, sites will document progressive disease or relapse as soon as possible and within 48 hours. The primary reason for discontinuation of study treatment is to be recorded in the eCRF. For all participants, the Sponsor should be informed as soon as progressive disease or relapse from CR/CRi/CRh is confirmed. Discontinuation criteria for all participants must be reviewed and confirmed by the Sponsor prior to discontinuation.

Investigator’s disease assessments will be used for response in Part 1 . Overall best response across all cycles of treatment will be used to assess response rate. For an overall best response of stable disease, disease stabilization must have lasted for at least 3 months.

Table 6: Response Assessments based on ELN 2017 (Dohner 2017)[6]

Category	Definition
Complete response (CR)	Bone marrow blasts <5%; absence of circulating blasts[a] and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count ≥1.0 × 10^9/L (1000/μL); platelet count ≥100 × 10^9/L (100 000/μL)
CR with incomplete recovery (CRi)	All CR criteria except for residual neutropenia (absolute neutrophil count <1.0 × 10^9/L [1000/μL]) or thrombocytopenia (platelets <100 × 10^9/L [100 000/μL])
CR with partial hematological recovery (CRh)*	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >0.5 × 10^9/L [500/μL] and platelet count >50 × 10^9/L [50, 000/μL]
CR without MRD (CR_{MRD-})	CR without MRD; defined as less than 1 blast or leukemic stem cell in 1,000 leukocytes (MRD level <10^{-3}; determined by central lab)
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial response (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Stable disease	Absence of CR, CRi, CRh, PR, MLFS and criteria for progressive disease not met
Relapse after CR, CRi, CRh	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease
Progressive Disease	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in bone marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline or; • Persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (>0.5 × 10^9/L [500/μL], and/or platelet count to >50 × 10^9/L [50 000/μL] nontransfused) or; • >50% increase in peripheral blasts (WBC x % blasts) to >25 × 10^9/L (>25000/uL) (in the absence of differentiation syndrome) or; • New extramedullary disease

* If both CRi and CRh criteria are met, CRh should be reported.
[a] Unless circulating blasts can be attributed to recent GCSF administration

The total blood volume to be collected from each participant will be between 700 to 770 mL, depending upon what samples are taken and assuming 8 cycles of treatment. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (USP) (or equivalent) and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator's Brochure (cusatuzumab); SPC or United States Package Insert for azacitidine
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual
- NCI-CTCAE Version 5.0
- PRO questionnaires
- EQ-5D-5L v 2 and FACT-Leu V 4
- IVRS/IWRS Manual
- eDC Manual
- Sample ICF

8.2. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Adverse Events and Serious Adverse Events Section 8.3 and Appendix 4 Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities:Table 1/Table 1A

8.2.1. Physical Examination

A full physical examination will be performed at screening. Subsequently, a directed physical examination (including all organ systems that were previously abnormal or involved with disease and documentation of any clinically relevant abnormalities in any organ) will be performed at the timepoints specified in the Schedule of Activities. Any changes that are clinically significant will be recorded on the AE eCRF. Height will be measured at Screening only; weight will be measured prior to the start of each cycle and at the EOT.

8.2.2. Vital Signs

Temperature, heart rate, respiratory rate, blood pressure will be recorded according to the Schedule of Activities (Table 1/Table 1A). Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones) and be monitored with the same method and position (sitting or supine) throughout the study.

8.2.3. Electrocardiogram

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

8.2.4. Spirometry Test

Participant's baseline pulmonary disease must have a spirometry test during the Screening Phase and then repeat evaluation per the Schedule of Activities Table 1/Table 1A.

8.2.5. ECOG Performance Status

The ECOG Performance Status scale will be used to grade changes in the participant's daily living activities. The ECOG Performance Status scale is provided in Appendix 6 Section 10.6. The frequency of ECOG Performance Status assessment is provided in the Schedule of Activities Table 1/Table 1A.

8.2.6. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Appendix 2 Section 10.2, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

The following laboratory elevations may indicate severe liver injury (possible Hy's law) and further workup and testing should be strongly considered. See Section 6.6 for study treatment dose modification guidelines.

- For participants with normal baseline AST, ALT and bilirubin, all events of AST or ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN
- For participants with baseline ALT or AST □3 × ULN, all events with ALT or AST □3 times baseline values in the absence of concurrent bilirubin elevations or new symptoms
- For participants with baseline ALT or AST □3 × ULN, all events with ALT or AST □2 × baseline values if concurrent bilirubin elevations or symptoms occur or no alternative causes are found.
- For participants with baseline bilirubin ≥2 × ULN, all events with bilirubin ≥2x baseline

8.3. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures. Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative).

For further details on adverse events and serious adverse events (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Appendix 4 Section 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study intervention or until the start of subsequent anti-AML therapy, if earlier. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The Sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate Sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the Sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the Sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local at the injection site and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the participant is not specifically questioned. Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrence.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The Sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or Sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/ Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.3.5. Adverse Events of Special Interest

Grade ≥3 IRR will be followed as part of standard safety monitoring activities by the Sponsor. These events will be reported to the Sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious adverse events) following the procedure described above for serious adverse events and will require enhanced data collection.

8.3.6. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the Sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must withhold treatment of the study intervention and notify the Sponsor's clinical team. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.4. Treatment of Overdose

For this study, any dose of cusatuzumab greater than 20 mg/kg, within a 24-hour time period will be considered an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Sponsor immediately. The Sponsor's clinical team will evaluate the extent of an overdose and will determine if the measures outlined below should be followed.

- Closely monitor the participant for AE/SAE and laboratory abnormalities for a minimum of 90 days.
- Obtain a serum sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Serum samples will be used to evaluate the PK of cusatuzumab. In addition, limited bone marrow aspirates may be used to evaluate cusatuzumab concentration in bone marrow. Limited plasma samples will be used to evaluate PK of azacitidine. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.5.1. Evaluations

Venous blood samples of approximately 7 mL will be collected for measurement of serum concentrations of cusatuzumab and anti-cusatuzumab antibodies as suggested in the Schedule of Activities (Table 1/Table 1A). In addition to serum samples, plasma samples will be analyzed for measurement of azacitidine concentrations.

Venous blood samples will be collected and each serum sample will be divided into 4 aliquots. Samples collected for analyses of cusatuzumab serum concentration and antibodies to cusatuzumab may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, for further characterization of immunogenicity or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

8.5.2. Analytical Procedures

Pharmacokinetics

Plasma and serum samples will be analyzed to determine concentrations of azacitidine and cusatuzumab, respectively, using validated, specific, and sensitive (eg, immunoassay and LC-MS/MS) methods by or under the supervision of the Sponsor. Additionally, concentrations of cusatuzumab in bone marrow will be determined for a small number of participants.

Immunogenicity

The detection and characterization of anti-cusatuzumab antibodies will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for

detection of anti-cusatuzumab antibodies will also be evaluated for cusatuzumab serum concentration to enable interpretation of the antibody data.

Anti-cusatuzumab antibodies will be evaluated in serum samples collected from all participants according to the Schedule of Activities. Additionally, serum samples should also be collected at the final visit from participants who are discontinued from intervention or withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to cusatuzumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of cusatuzumab.

Serum samples will be used to evaluate the immunogenicity of anti-cusatuzumab antibodies. Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Receptor Occupancy

Whole blood samples will be analyzed for RO via flow cytometry.

8.5.3. Pharmacokinetic Parameters and Evaluations

Parameters

Based on the individual serum concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of cusatuzumab will be derived using population PK modelling. Baseline covariates (eg, body weight, age, sex, CrCL, race) may be included in the model, if relevant.

Pharmacokinetic/Pharmacodynamic Evaluations

If sufficient data are available, pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of cusatuzumab and biomarkers, PD markers, or endpoints of clinical efficacy. If these analyses are performed, the details and results will be presented in a separate report.

8.6. Genetics

Genetics are not evaluated in this study, however, somatic mutations are evaluated in the tumor cells as described in Section 8.8.

8.6.1. Cytogenetics/ Mutational Analysis

Assessment of mutational status must be performed per schedule of activities (Table 1/Table 1A) and must include testing for all mutations listed in Appendix 10. Central and/or local testing is acceptable. Bone marrow collected at screening is preferred for mutational analyses. However, standard-of-care assessment of mutational status obtained prior to the ICF signing will be accepted in lieu of screening marrow, provided that it includes testing for all mutations listed in Appendix

10. Left over fresh or frozen bone marrow samples may be requested for central mutational analysis if all tests are not performed by the local study site.

8.7. Pharmacodynamics

Samples of bone marrow aspirates or whole blood for pharmacodynamics evaluations will be collected as specified in the Schedule of Activities Table 2. Biomarker tests will include, but not limited to: evaluation of CD70 and CD27 expression level and decrease numbers of blasts and leukemia stem cells (LSC) in whole blood and bone marrow by flow cytometry, mRNA levels for CD70, CD27 and other CD70-CD27 signaling-related genes, and LSC gene signature by transcriptome analysis. Serum samples will be collected and used for protein quantification for evaluation of soluble CD27 and may be for inflammatory cytokines. The changes in pharmacodynamic parameters from baseline to timepoints specified in the Schedule of Activities (Table 2) will be analyzed.

8.8. Biomarkers

Samples for biomarker evaluations will be collected as specified in The Schedule of Activities Table 2. The baseline levels and changes from baseline in biomarkers will be analyzed. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

The biomarkers to be tested in this study are based on the cusatuzumab mechanism of action, treatment with cusatuzumab results in induction of cytotoxicity against CD70-positive tumor cells by antibody effector mechanisms (enhanced ADCC, ADCP, CDC), by blocking proliferation and survival signals of malignant cells, and by induction of an anti-tumor immune response following interruption of CD70-CD27 signaling. The approaches of biomarker tests include, but not limited to, the following:

Flow cytometry/ CyTOF: The main mechanism of action of cusatuzumab is ADCC through NK cell activation, therefore, bone marrow aspirates or whole blood will be analyzed for immunophenotyping by flow cytometry for NK cell counts and biomarker of NK cell activation. In addition, B cells, T cell subsets, and other immune cell subpopulations, such as activated T cells, Treg, may be evaluated by flow cytometry and/or CyTOF. An additional mechanism of action may be through the induction of myeloid differentiation. Bone marrow aspirates will be evaluated for markers of differentiation by flow cytometry. These assessments will be evaluated for the association with clinical outcome.

Genomic analysis: DNA sequencing from tumor cells will be performed to identify mutations for characterization of disease subtype and potential predictive biomarkers of response and resistance. DNA methylation analysis may be performed.

Gene expression/transcriptome profile: RT-PCR or RNAseq analysis for evaluating the effect of cusatuzumab plus azacitidine on mRNA levels of CD70, CD27, genes involved in CD70/CD27 signaling pathways, and leukemic stem cell (LSC) signature. Baseline transcriptome profile will be correlated to clinical response to identify gene signatures potential predict response to

cusatuzumab plus azacitidine.

Minimal/measurable residual disease (MRD) assessment: MRD assessments will be performed on bone marrow aspirates and whole blood samples collected from all participants at baseline by flow cytometry and molecular methods such as next generation of sequence (NGS) or droplet PCR to establish the clone for MRD monitoring. Additional bone marrow aspirate and whole blood sample will be taken for participants at suspected CR, then follow up until relapse or EOT to assess duration of MRD negativity. For flow cytometry MRD assay, the cutoff for MRD negativity is defined as less than 1 blast in 1,000 leukocytes (MRD level $<10^{-3}$ as recommended by the ELN.[6] In addition, other lower cutoff values will be evaluated for MRD negativity.

Additional Collections

Additional blood samples will be collected if a participant experiences Grade 3 or greater infusion-related reactions for cytokine analysis. If it is determined at any time before study completion that additional material is needed for the successful completion of the protocol-specified analyses, the Sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the Sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study intervention(s) or diseases being investigated.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

8.9. Patient-Reported Outcomes

Patient-reported outcome assessments will be conducted as described in the Schedule of Activities (Table 1/Table 1A). Patient-reported outcome assessments should be completed at the beginning of the corresponding assessment, before any other assessments, examinations, or treatments following the PRO completion guidelines.

Patient-reported outcome instruments will be administered on paper forms to be filled out directly by the participant, except in the cases of follow-up assessments that may be conducted by telephone or under special circumstances as described in the PRO completion guidelines (eg, assisted administration for participants with visual impairment). In the event that PRO assessments cannot be completed as scheduled during a site visit it should be entered in the eCRF.

Patient-reported outcome instruments included in this study are the Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) and EuroQoL 5 Dimension 5 Level questionnaire (EQ-5D-5L).

The FACT-Leu is a 44-item instrument measuring health-related quality of life concepts. It is comprised of 4 subscales that make up the FACT-G: physical well-being (PWB, 7 items), social/family well-being (SWB, 7 items), emotional well-being (EWB, 6 items), and functional well-being (FWB, 7 items) and a fifth subscale for leukemia-specific concerns (LeuS, 17 items). Items are rated on a response scale from 0 (not at all) to 4 (very much). Subscale and total scores may be calculated according to instrument administration and scoring guidelines; higher scores indicated better health-related quality of life.

The EQ-5D consists of 5 items describing health state and the EuroQoL visual analog scale (VAS) of self-rated overall health. Responses for the 5 descriptive items are converted into a single index value or utility score according to EQ-5D scoring algorithm ranging from -1 to 1 where lower scores indicate worse health status. EQ-5D-VAS responses range from 0 (the worst health you can imagine) to 100 (the best health you can imagine).

Minimum important difference (MID) thresholds for improvement/worsening will be specified in the statistical analysis plan for any PRO score analyses requiring a threshold. All PRO scale scores will be calculated according to published instrument manuals (ie, administration and scoring guidelines) for scoring and handling of missing data unless otherwise specified.

8.10. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration and reasons for medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications) and reasons

9. STATISTICAL CONSIDERATIONS

Detailed statistical methods used in the study design are described in this section. Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypotheses

The primary hypothesis is that participants treated with the combination of cusatuzumab (at a dose level of 10 mg/kg or 20 mg/kg) and azacitidine can achieve a CR rate of 35% or greater against the null hypothesis of 20%.

9.2. Sample Size Determination

Up to 50 participants will be enrolled for each dose group in Part 1 of the study. Part 1 will utilize a 3-stage monitoring approach to determine, at each stage and for each dose group, if the observed CR rate warrants the respective dose to be continued into the next stage or into Part 2 of the study (see details in Section 9.5, Interim Analysis). Participants will be enrolled into Part 2 at the selected cusatuzumab dose until a cumulative total of 100 participants have been treated with the selected dose from Part 1 and Part 2. The study has a >90% power to reject the null hypothesis of a CR rate of 20% under the alternative hypothesis of 35% for a total of 100 participants (from Part 1 and Part 2) at the selected dose level. This sample size is based on the single-arm Wilson Score test without continuity correction at an overall 1-sided type 1 error rate <2.5%.

9.3. Populations for Analyses

The primary analysis of efficacy will be based on the intent-to-treat (ITT) population that includes all randomized (Part 1) and all enrolled (Part 2) participants. Selected efficacy endpoints will also be performed on the efficacy-evaluable population that includes all ITT participants who have baseline and at least one post-baseline disease evaluation. Safety will be evaluated on the safety population that includes all participants who have received at least 1 dose of study intervention. The pharmacokinetic analyses will be performed on the pharmacokinetic evaluable population.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

Binary endpoints will be summarized with number and percentage of participants achieving the endpoint along with the corresponding 2-sided 95% exact confidence interval. These endpoints include CR, CR + CRh, CR+CRh+CRi, CR without MRD, MRD negativity, and transfusion independence. Hypothesis testing for the primary endpoint of CR rate will be performed using the Wilson Score test without continuity correction against the null hypothesis of 20% at the planned interim and final analyses (see Section 9.5, Interim Analysis).

The Kaplan-Meier method will be used to summarize time-to-events endpoints, including time to CR, time to CR + CRh + CRi, duration of CR, duration of CR+ CRh + CRi, PFS, and OS. Time to and duration of response are defined only for participants who achieved such responses; PFS and OS are defined for all participants. Duration of transfusion independence will also be summarized for participants who achieved such status.

No formal hypothesis testing or formal statistical comparison between the 2 dose groups is planned for study Part 1.

9.4.2. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Toxicities will be graded for severity according to NCI-CTCAE, version 5.0. Intervention-emergent adverse events are adverse

events with onset during the intervention phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

Specifically, the following will be summarized:

- All adverse events;
- Grade 3 or higher adverse events;
- Serious adverse events;
- Adverse events leading to discontinuation of treatment;
- Adverse events leading to death; and
- Adverse events of special interest.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an adverse event, or who experience a severe or a serious adverse event.

Parameters with predefined National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the participant during the study will be provided as shift tables.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline. Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the participants during the study will be provided as shift tables.

Electrocardiogram (ECG)

Electrocardiogram data will be presented by descriptive analysis only.

Physical Examination

Clinically significant abnormal physical examination changes will be recorded and summarized as adverse events.

9.4.3. Other Analyses

A Data Review Committee (DRC) will be established as noted in Committees Structure in Appendix 3 Section 10.3 Regulatory, Ethical, and Study Oversight Considerations.

Pharmacokinetic Analyses

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for cusatuzumab and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date and may be included in a population PK re-analysis when they become available after database lock.

Data will be listed for all participants with available serum concentrations per intervention group. Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report.

For each intervention group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters including exposure information of cusatuzumab.

All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or SAS dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All participants and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Descriptive statistics will be used to summarize cusatuzumab serum concentrations at each sampling time point and PK parameters of cusatuzumab: C_{min} and C_{max}. Other PK parameters, including but not limited to $AUC_{(t1-t2)}$, $t_{1/2}$, CL, and V, when available, will also be summarized.

Mean and or median serum cusatuzumab concentration time profiles will be plotted after the first dose of study intervention, and individual serum concentration time profiles may also be plotted.

If sufficient data are available, population PK analysis of serum concentration-time data of cusatuzumab will be performed using nonlinear mixed effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report. Exposure-response analyses may also be performed; if performed, details will be provided in a separate analysis plan and report.

Biomarker Analyses

The biomarker measures will be listed, tabulated, and where appropriate, plotted. Participants may be grouped by dose, or clinical endpoints. Analyses may be stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance [ANOVA], or survival analysis, depending on the

endpoint). Correlation to clinical response may be explored to identify markers predictive of response (or resistance) to cusatuzumab and azacitidine combination treatment.

Results of biomarker analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

Immunogenicity Analyses

The incidence of anti-cusatuzumab antibodies will be summarized for all participants who receive at least 1 dose of cusatuzumab and have appropriate samples for detection of antibodies to cusatuzumab (ie, participants with at least 1 sample obtained after their first dose of cusatuzumab).

A listing of participants who are positive for antibodies to cusatuzumab will be provided. The maximum titers of antibodies to cusatuzumab will be summarized for participants who are positive for antibodies to cusatuzumab.

The incidence of neutralizing antibodies (NAbs) to cusatuzumab will be summarized for participants who are positive for antibodies to cusatuzumab and have samples evaluable for NAbs to cusatuzumab.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

Pharmacodynamic Analyses

The pharmacodynamic biomarker measures will be listed, tabulated, and where appropriate, plotted. Changes in sCD27, blasts, LSCs, or gene expression over time from baseline will be summarized for groups by dose, or clinical endpoints.

Patient-Reported Outcomes

Total and subscale scores from the PRO instruments listed in Section 8.1 will be analyzed: EQ-5D-5L utility score, EQ-5D-VAS score, FACT-Leu Total, PWB, SWB, EWB, FWB, FACT-G, FACT-LeuS, FACT-Leu TOI.

For each scale score descriptive statistics (mean, standard deviation, median, and range) will be calculated for each assessment time point, for change from baseline at each time point, and for change from previous time point.

Mixed-model repeated measures will be used for longitudinal analyses of PRO score change over time for each subscale. Time-to-event analyses will also be conducted using the Kaplan-Meier method using specified MID thresholds to define time-to-worsening and time-to-improvement for each PRO scale score.

Medical Resource Utilization Analyses

Medical resource utilization will be descriptively summarized by intervention group.

9.5. Interim Analyses

For each analysis (3 stages in Part 1 and the formal interim and final analysis in Part 2), the data cutoff will be the time point when the last participant in the respective analysis has been treated for a minimum of 3 cycles (Part 1) or 4 cycles (Part 2) of the combination therapy.

NOTE: Part 2 of the study will not be conducted because further development of this regimen (cusatuzumab in combination with azacitidine) in patients with unfit AML will not be pursued due to the evolving treatment landscape in AML.

Study Part 1

Part 1 of the study consists of 3 stages of monitoring to select a dose schedule. The cumulative number of participants for each dose group at each of the 3 stages are 15, 30, and 50, respectively. At each stage, each dose group's response rate will determine independently (without formal statistical comparison to the other group) if that dose group will be stopped or continued into the next stage or into study Part 2. Only 1 dose group will be selected for Part 2. The statistical criteria for such a determination will be based on the number (and percentage) of participants in each dose group achieving CR.

The purpose of the 3-stage monitoring in Part 1 is to select, or to eliminate a dose, which will be based on the Pocock beta-spending function with an overall beta level of 10% allocated to the 3 stages with respective and cumulative sample sizes of 15 (30%), 30 (60%), and 50 (100%) participants per group. Per this approach, the statistical decision criteria and corresponding inferences are summarized in Table 7, where 2 possible outcomes resulting in a stop or continuation decision, respectively, are presented for each stage.

The statistical criteria shown in Table 7 ensure that the false negative error rate (ie, the probability of a stopping decision, when the true CR rate is ≥35%) is ≤6% at any stage; or equivalently, the upper limit of the 1-sided >94% confidence interval (CI) of the observed CR rate is <35% (which means that a CR rate of 35% or greater has been statistically ruled out). It's important to control the false negative error rate at a low level when the number of participants is small to ensure that a stopping decision will not be made unless it is statistically convincing that a CR rate of ≥35% has been ruled out. The false positive error rate (ie, the probability of a continuation decision, when the true CR rate is ≤20%) is also assessed, but controlling the false positive error rate at a low level is not of a concern, hence is not applied in this circumstance (Table 8).

Table 7: Statistical Decision Parameters for Study Part 1: Observed CR, 1-Sided Confidence Interval (CI), and Statistical Decision

	Number (%) of Observed CR	1-Sided CI Upper Bound[1] (%)	Decision	False Negative Error[2]	False Positive Error[3]
Stage 1, n=15	1 (6.7)	26.7	Stop	≤4%	NA
	2 (13.3)	34.9			
	3 (20.0)	42.3	Continue to Stage 2	NA	≤50%
	4 (26.7)	49.3			
Stage 2, n=30	5 (16.7)	30.5	Stop	≤5%	NA
	6 (20.0)	34.3			
	7 (23.3)	37.9	Continue to Stage 3	NA	≤32%
	8 (26.7)	41.5			
Stage 3, n=50	11 (22.0)	32.3	Stop	≤6%	NA
	12 (24.0)	34.4			
	13 (26.0)	36.6	Continue to Part 2	NA	≤14%
	14 (28.0)	38.7			

[1] 96%, 95%, and 94% for Stage 1, 2, and 3, respectively.
[2] False negative error: probability of a "stop" decision, when the true CR rate is ≥35%.
[3] False positive error: probability of a "continue" decision, when the true CR rate is ≤20%.
Note: All statistical inferences are based on Wilson Score statistics without continuity correction.

If the number of participants at each stage is not exactly as specified in Table 7 the Pocock beta-spending function with an overall beta level of 10% will be adjusted based on the actual number participants.

Per statistical criteria specified in Table 7, certain operating characteristics of particular interest are presented in Table 8, showing the probability of making a correct decision.

The above statistical criteria for Part 1 will be served as guidance; the totality of the data including other efficacy outcomes (eg, duration of CR), available safety, and PK/PD data will be considered in making a decision at each stage. If both dose schedules warrant proceeding into study Part 2 per the above statistical criteria, only one dose schedule will be extended into Part 2 based on the observed CR rate as well as available data of other efficacy, safety, and PK/PD.

Table 8: Operating Characteristics of Particular Interest

	True CR Rate of Dose (20 mg/kg, 10mg/kg)		
Study Part 1, probability that:	**(35%, 35%)**	**(35%, 20%)**	**(20%, 20%)**
At least one dose schedule continues into Part 2	98.4%	--	--
20 mg/kg continues into Part 2, 10 mg/kg does not	--	74.3%	--
Neither dose schedule continues into Part 2	--	--	72.1%

Study Part 2

For study Part 2, one interim analysis of CR rate is planned to include 80 participants. The null hypothesis of a CR rate of 20% will be rejected if the 1-sided nominal p-value is ≤0.01221. If the null hypothesis is not rejected at this interim analysis, the final analysis will be performed with 100 participants, and the null hypothesis will be rejected if the 1-sided nominal p-value is ≤0.02144. The O'Brien-Fleming alpha-spending, and the Wilson Score test without continuity correction are to be implemented for the interim and final analyses.

9.6. Data Review Committee

A Data Review Committee (DRC) will be established as noted in Committees Structure in Appendix 3 Section 10.3, Regulatory, Ethical, and Study Oversight Considerations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ATRA	all-trans retinoic acid
AUC	area under the concentration x time curve
BSA	body surface area
CDC	complement-dependent cytotoxicity
Cl	clearance
Cmax	maximum concentration
CR	complete response
CRh	complete response with incomplete hematological recovery
CRi	complete response with incomplete blood count recovery
CyTOF	time of flight mass cytometry
DRC	data review committee
DNMT	DNA methyltransferase
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case report form
ELN	European Leukemia Network
EOT	end-of-treatment
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia
FSH	follicle stimulating hormone
HIV	human immunodeficiency virus
HMA	hypomethylating agent
HRQoL	health-related quality of life
HRT	hormonal replacement therapy
ICF	informed consent form
IRR	infusion-related reaction
ITT	intent-to-treat population
IV	intravenous
LSC	leukemic stem cell
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia-free state
MRD	minimal residual disease
MRU	medical resource utilization
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer (cells)
ORR	overall response rate (CR + CRi + CRh)
OS	overall survival
PCR	polymerase chain reaction

PD	pharmacodynamics
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PRO	patient-reported outcome
RO	receptor occupancy
SAE	serious adverse event
SC	subcutaneous
SPC	Summary of Products Characteristics
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
USPI	United States Package Insert
WBC	white blood cells

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the local laboratory:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Platelet count Hemoglobin Absolute white blood cell (WBC) count Absolute eosinophils Absolute basophils Absolute monocytes Absolute neutrophil count Absolute lymphocyte count Peripheral blast count
Clinical Chemistry	Sodium Bicarbonate Potassium Blood urea nitrogen (BUN) Urea (if BUN is not performed) Creatinine Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic Total bilirubin Alkaline phosphatase Lactic acid dehydrogenase (LDH) Uric acid Calcium Phosphate Magnesium
Other Screening Tests	Serum β-hCG or urine pregnancy testing for women of childbearing potential only or if clinically indicated or required by local regulations. Serology (eg, HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B virus antibody, and hepatitis C virus antibody); screening is to be performed for all participants.

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Counsel on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the Sponsor will modify this protocol without a formal amendment by the Sponsor. All protocol amendments must be issued by the Sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the Sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate Sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the Sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the Sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or Sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or Sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

Each participant (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized Sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable

representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the participant's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

If the participant or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant or legally acceptable representative is obtained.

When prior consent of the participant is not possible and the participant's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the participant and to ensure compliance with applicable regulatory requirements. The participant or legally acceptable representative must be informed about the study as soon as possible and give consent to continue.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory PD, biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the Sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand cusatuzumab, to understand AML, to understand differential intervention responders, and to develop tests/assays related to cusatuzumab and AML. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

COMMITTEES STRUCTURE

Data Review Committee

A DRC will be established to monitor data on an ongoing basis and to review interim data to ensure the continuing safety of the participants enrolled in this study and to meet efficacy objectives. This committee will consist of at least one medical expert in the relevant therapeutic area, at least one statistician, and a minimum of 2 investigators that will participate in the CULM20236 study; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review interim data. After the review, the DRC will make recommendations regarding the continuation of the study.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding cusatuzumab or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the Sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the Sponsor in connection with the continued development of cusatuzumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the Sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the Sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the Sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the Sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The Sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the Sponsor Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The Sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the Sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the Sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or Sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the Sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

MONITORING

The Sponsor will use a combination of monitoring techniques: central, remote, or on-site monitoring to monitor this study.

The Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician’s office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the

eCRF are known to the Sponsor and study-site personnel and are accessible for verification by the Sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The Sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the Sponsor as requiring central review.

ON-SITE AUDITS

Representatives of the Sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the Sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the Sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period

if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The Sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event

must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For cusatuzumab, the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For azacitidine with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the SPC or USPI.

Adverse Event Associated With the Use of the Intervention

An adverse event is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An adverse event that is not related to the use of the intervention.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant treatment(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the intervention. An alternative explanation, eg, concomitant treatment(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the intervention. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant treatment(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant treatment(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

SEVERITY CRITERIA

Adverse events will be graded by the investigator according to NCI-CTCAE, Version 5.0.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to adverse event.

Activities of Daily Living:
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a Sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study intervention
- Suspected abuse/misuse of a Sponsor study intervention
- Accidental or occupational exposure to a Sponsor study intervention
- Medication error involving a Sponsor product (with or without participant/patient exposure to the Sponsor study intervention, eg, name confusion)
- Exposure to a Sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local Sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- If the participant has not experienced a significant medical event but is hospitalized overnight only for observation following injection of study intervention, then the hospitalization should not be reported as an SAE
- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

Expected progression of disease should not be considered an adverse event (or serious adverse event). However, if determined by the investigator to be more likely related to the study intervention than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study intervention is enhancing disease progression, should be reported per the usual reporting requirements.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the Sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the Sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse

Event Information). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.6, Pregnancy and Appendix 4 Section 10.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

All initial reports of pregnancy must be reported to the Sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Because the effect of the study intervention on sperm is unknown, pregnancies in partners of male participants included in the study will be reported as noted above.

10.6. Appendix 6: ECOG Performance Status Score

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken 1982[20]

10.7. Appendix 7: New York Heart Failure Criteria

The following table presents the New York Heart Association classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease

10.8. Appendix 8: Patient-reported Outcomes FACT-Leu Questionnaire

FACT-Leu (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
BRM2	I am bothered by the chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU5	I feel uncertain about my future health	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4

10.9. Appendix 9: Patient-reported Outcomes EQ-5D-5L Questionnaire

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

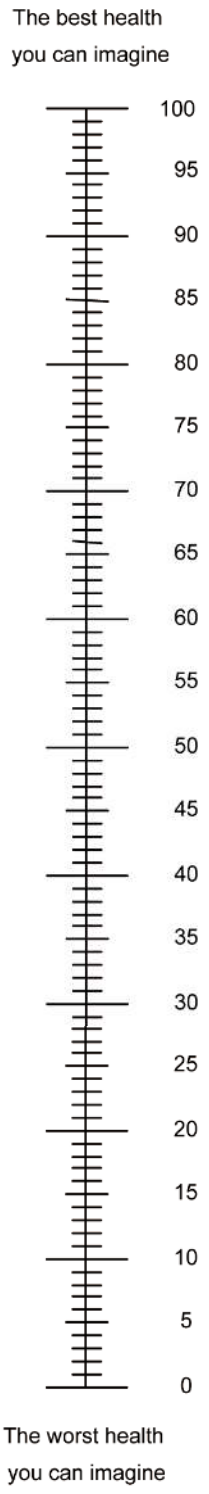
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY= ☐



10.10. Appendix 10: Risk Stratification by Genetics

Assessment of mutational status must be performed and must include testing for **all** mutations listed below (Table 9). Central and/or local testing is acceptable. Bone marrow collected at screening is preferred for mutational analyses. However, standard-of-care assessment of mutational status obtained prior to the ICF signing will be accepted in lieu of screening marrow, provided that it includes testing for all mutations outlined below. Left over fresh or frozen bone marrow samples may be requested for central mutational analysis if all tests are not performed by the local study site.

Table 9: ELN Risk Stratification by Genetics[6]

Risk Category[a]	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low b]
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITDhigh[b]
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low b] (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[c]
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	25 or del(5q); 27; 217/abn(17p)
	Complex karyotype,[d] monosomal karyotype[e]
	Wild-type *NPM1* and *FLT3-ITD*[high b]
	Mutated *RUNX1*[f]
	Mutated *ASXL1*[f]
	Mutated *TP53*[g]

AML=Acute myeloid leukemia; ELN=European LeukemiaNet; HCT=hematopoietic cell transplant; WHO=World Health Organization

Footnotes:

a. Prognostic impact of a marker is treatment-dependent and may change with new therapies
b. Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of FLT3-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "FLT3-ITD" divided by area under the curve "FLT3-wild type"; recent studies indicate that AML with NPM1 mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT.
c. The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
d. Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.
e. Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).
f. These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
g. *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

10.11. Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 3 (30 September 2021)

Overall Rationale for the Amendment: After 22 Oct 2021 (after the primary endpoint analysis had been completed), subjects who are still benefiting from study treatment can continue to receive study treatments and will have a reduced schedule of assessments.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) Table 1	Note was added indicating that after 22 Oct 2021, subjects will no longer be treated and assessed per Table 1 but will follow reduced schedule of assessments per Table 1A.	Modified timing of blood sample collection/analyses and assessments to reduce burden for ongoing study participants
1.3 Schedule of Activities (SoA) Table 1A	A new SoA table was added limiting the number of assessments. Minimal residual disease analysis is included in Table 1A. Bone marrow: every 4 cycles following CR and every 2 cycles following complete response with incomplete blood count recovery (CRi)/ complete response with partial hematological recovery (CRh) (collected between Day 21 up to and including Day 1 of the next cycle). Whole Blood: Every 2 cycles following CR/CRi/CRh on Day 1. A note was added that for participants who discontinue study treatment without disease progression, disease evaluations should continue with the same frequency as during study treatment until disease progression or start of subsequent therapy, whichever occurs first.	
Synopsis; 1.3 Schedule of Activities (SoA); Table 2; Table 3; Table 4; Table 5; Section 4.1	Note was added that after 22 Oct 2021, blood samples for pharmacodynamic, biomarker, and pharmacokinetic analysis will not be collected.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	To provide clarity.

Amendment 2 (19 August 2020)

Overall Rationale for the Amendment: This amendment removes Part 2 of the study and addresses feedback from the investigators on the timing of disease assessments and use of anti-infective prophylaxis.

Section Number and Name	Description of Change	Brief Rationale
Synopsis: Overall Design, Treatment Groups and Administration, Statistical Methods; 1.2 Schema; 2.1.1 Study Design Rationale; 4.1 Overall design; 4.2 Scientific Rationale for Study Design; 9.2 Sample Size Determination; 9.5 Interim Analyses	Added language indicating Part 2 of the study has been removed; deleted language pertaining to Part 2	Further development of cusatuzumab in combination with azacitidine alone will not be pursued
Synopsis: Treatment Groups and Administration; 4.4. End of Study Definition	Changed end-of-study definition. It will be reached when all subjects have completed or discontinued study treatment.	Clarified study procedures
Synopsis: Efficacy Evaluations; 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 8.1 Efficacy Assessments; 9.4.1. Efficacy Analyses; 10.1 Appendix 1 Abbreviations and Trademarks	Deleted language referring to the IRC	IRC is no longer needed as it was planned to only be established for Part 2
1.3 Schedule of Activities Table 1	Clarified Cytogenetic testing also included Mutational analysis; added footnote d.	Clarified study procedures
1.3 Schedule of Activities Table 1	Modified disease evaluation to be performed until CR or progressive disease (deleted CRi and CRh); clarified in cases of cycle delays, timing of disease evaluations should be performed per protocol at the end of the specified odd cycle.	To provide clarity on the frequency of disease evaluations and study procedures
2.1.5 Rationale for Administration Schedule	Modified language to describe azacitidine dosing in all cycles is on Day 1 through Day 7	
6.1 Study Interventions Administered	Modified language to clarify that in the absence of IRRs, subsequent infusions with cusatuzumab are to be administered at the highest rate in the preceding infusion	
6.1.2 Anti-infective Prophylaxis; 6.5.1 Permitted Therapies	Described anti-infective prophylaxis per ELN recommendations	

Section Number and Name	Description of Change	Brief Rationale
6.6.1 Management Guidelines for Potential Toxicities During Cusatuzumab Infusion	Modified language regarding infusion rate for subjects that do not experience IRR symptoms after a Grade 3 IRR	
8.1 Efficacy Assessments	Added footnote to Table 6 to clarify CR definition with the absence of circulating blasts unless they can be attributed to GCSF administration	
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Stipulated that adverse event reporting is performed until 30 days after the last dose of study intervention or until the start of subsequent anti-AML therapy, if earlier.	
8.6.1 Cytogenetics; 10.10 Appendix 10: Risk Stratification by Genetics	Added section with description of cytogenetic testing for mutational status	
10.2 Appendix 2: Clinical Laboratory Tests	Added clinical laboratory assessment for Urea	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 1 (22 October 2019)

Overall Rationale for the Amendment: To address comments from health authorities and to provide additional clarity

Section number and Name	Description of Change	Brief Rationale
Synopsis; 9.2 Sample Size Determination	Modified description of numbers of participants	To provide clarity
Schedule of Activities Table 1	Added cytogenetic testing at screening; Increased the frequency of hematology and chemistry monitoring; deleted additional monitoring of chemistry for participants with baseline ALT/AST elevations because all participants will have increased monitoring; added footnote "m" to permit sampling within 24 hours of the Day 1 and Day 17 visits; added language to column header to describe first follow-up visit at 30 days after last study treatment; added footnote "b" to reinforce that all adverse events are reported until 30 days after the last dose of study intervention; clarified that pregnancy testing should be done at each cycle visit, at the end-of-treatment visit, and (footnote "n") 1 month after the last dose of study treatment; removed stipulation of disease evaluation within 7 days of Cycle 1 Day 1, added starting at Cycle 1 following phrase "every other cycle"; modified footnote "f" to clarify that disease evaluations should continue for participants who discontinue treatment without disease progression; added footnote "g" for disease assessments to include 2-3 peripheral blood samples for blast counts at screening; modified footnote "h" to stipulate that bone marrow aspirates are to be sent to the central laboratory within 48 hours for biomarker and PK testing; relettered footnotes.	To increase monitoring of participants and define first follow-up visit; added footnotes to provide clarity.
Schedule of Activities Table 1; Appendix 2 Clinical Laboratory Tests	Deleted coagulation testing; Modified footnote "o" to change testing for hepatitis and HIV at screening to make it mandatory for all participants	Removed unnecessary laboratory assessments to reduce burden on study participants.
Schedule of Activities Table 1; 8.1 Efficacy Assessments	Footnote "h": removed the words "bone marrow biopsy" from associating with biomarkers and PK samples	Clarified that bone marrow biopsy or aspirate can be used for morphology assessment; however, biomarker and PK testing require aspirate

Section number and Name	Description of Change	Brief Rationale
Schedule of Activities Table 2 8.8. Biomarkers	Added MRD assessment to flow cytometry column; added column for DNA sequencing; added assessments for flow cytometry/CyTOF/MRD on bone marrow and blood samples, protein quantification, and gene expression at every disease evaluation; changed Cycle 1 Day 3 sampling to Day 2; Footnote "a": added "samples stored for future analysis"; removed whole blood sample at screening for gene expression. Explained that the bone marrow aspirate sample will also be used for myeloid differentiation assay.	Aligned the schedule of biomarkers assessment with that of disease evaluations Clarified that MRD assessments will be done upon assay availability To inform regarding mechanism of action of cusatuzumab
Schedule of Activities Table 3	Cycle 1 Day 7 assessments were removed; defined assessments for Cycles 2 to 5 and for odd cycles beginning with Cycle 7. Footnote "a": added "dependent upon assay availability"	Removed unnecessary sampling to reduce burden on participants. Clarified that PK/RO assessments will be done depending on the validated assay availability
Added Schedule of Activities Table 4	Separated timing for samples for pharmacokinetic evaluations for azacitidine to a unique table	To provide clarity
Schedule of Activities Table 5	Table 4 of original protocol becomes Table 5	To match sampling for participants after the 50th participant with participants randomized before the 50th participant
2.1.4 Rationale for Dose Selection	Text added to describe target concentrations and the proportion of patients who achieve this at each dose level being studied.	Provided additional clarity around available PK data and compartmental effect on PK to strengthen the dose selection rationale
2.2.2.1 Clinical Data	Removed the word "RP2D"	To provide further clarifications of the existing text
3. Objectives and Endpoints	Clarified the definition of time to response and duration of response; added the secondary endpoint of transfusion independence and its definition	To provide further clarification of the existing text Added relevant endpoint for AML studies
10.3 Appendix 3: Data Review Committee	Added language regarding membership and activities of the Data Review Committee	To further clarify membership and activities of the Data Review Committee
4.1 Overall Design; 9.5 Interim Analyses	Changed timing of data for DRC review to minimum of 3 cycles for Part 1 and 4 cycles for Part 2 from 4 cycles per participant; added language regarding activities of the DRC	To provide further clarification of the existing text

Section number and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	Clarified co-morbidity inclusion criterion; added hydroxyurea and changed low dose cytarabine to dose of cytarabine (1-2g/m^2) to exceptions for treatment; renumbered inclusion criteria with 3 bulleted items from criteria 2 in the original protocol placed as criteria 3 to 5; clarified contraceptive language; removed age restriction for definition of "postmenopausal"; added language to include legally acceptable representative in understanding the ICF; added criteria related to donation of eggs or sperm; added criteria related to fathering a child.	To manage hyperleukocytosis; to clarify inclusion criteria
5.2. Exclusion Criteria	Removed language defining genetic marker for APL; clarified that the immune suppressive agent administration should be terminated before the Cycle 1 Day 3 cusatuzumab dose; removed "untreated" from systemic infection exclusion criterion; removed "if tested" from HIV related exclusion criteria because all are tested; added instructions for treatment of adrenal insufficiency; added criterion to exclude women who are breastfeeding; modified criteria related to prior/current other malignancies; added criterion to exclude participants who received live attenuated vaccines; clarified criterion with regard to hepatitis B and C infection; clarified exclusion for major surgery 4 weeks prior to initiation of study.	Corrected day to match cusatuzumab dosing; clarified exclusion criteria; added exclusion criteria
5.3 Lifestyle Considerations	Added statement that male participants should inform fertile female partners to use effective methods of birth control.	To further clarify contraception instructions for male participants
6.1 Study Interventions Administered	Clarified that BSA and dose only be recalculated if there is a >10% change in body weight from previous calculation	To provide clarity
6.1.1 Premedications	Removed sentence stipulating that cusatuzumab premedications be given prior to azacitidine administration	To provide clarity
6.5 Concomitant Therapy	Removed need for non-pharmacologic therapies to be recorded in the eCRF	To eliminate unnecessary documentation
6.5.1. Permitted Therapies	Added text allowing certain treatments for non-AML malignancies; changed time period defining short-term corticosteroid use to ≤7 days	To add exemptions to prohibited medications
6.5.2 Prohibited Therapies and Procedures	Removed definition of short-term corticosteroid; added "treatment" after "study" to define period of time; added text allowing certain treatments for non-AML malignancies; removed language regarding ATRA treatment; removed cytoreduction language; added any other monoclonal antibody	To reduce redundancy; to restrict treatment with other therapies or procedures only during the period when participants are receiving study treatment; to add exemptions to prohibited medications

Section number and Name	Description of Change	Brief Rationale
6.5.3 Subsequent Anticancer Therapy	Removed stipulation that only the first anticancer therapy be documented	To provide clarity
6.6. Dose Modification; 6.6.2. Management Guidelines for Toxicities Attributed to Cusatuzumab	Divided section into 2 subsections (1 for cusatuzumab and 1 for azacitidine); removed the guidance allowing for cusatuzumab dose escalations or reductions; clarified that escalations and reductions are only allowed at the time of dose selection; changed wording from "must" to "should" in first bullet.	To provide clarity
6.6.1 Management Guidelines for Potential Toxicities During Cusatuzumab Infusion	Deleted Section 6.1.2 and moved to Section 6.6.1; changed title to reflect guidelines for toxicity management during cusatuzumab infusion; modified guideline to stipulate IRRs or hypersensitivity reactions.	For participant safety
6.6.3. Management Guidelines for Toxicities Attributed to Azacitidine	Added text for azacitidine dose reductions from the SPC	To provide clarity
6.7 Intervention After the End of Treatment	Changed title from end of the study to end of treatment	To reflect correct description of section
7.1 Discontinuation of Study Intervention	Removed bullet referring to discontinuation following initiation of treatment with a prohibited medication	To align with Section 6.5.2: Prohibited Therapies and Procedures which requires notification to the Sponsor for administration of any prohibited medications
8 Study Assessments and Procedures	Clarified that standard of care tests performed within the screening period but prior to signing the ICF can be used for eligibility	To provide clarity
8.1. Efficacy Assessments	Added methods of extramedullary disease evaluation. Changed total blood volume needed from participants	To provide further clarifications of the existing text Changes to PK and biomarker sampling warranted changes to total blood volume needed
8.4 Treatment of Overdose	Clarified Sponsor's clinical team will evaluate participants with suspected overdose	To correct language
8.6 Genetics	Added phrase "in tumor cells"	To stipulate that genetics is performed on tumor cell samples
9.3. Populations for Analysis	Differentiated between the Part 1 randomized and Part 2 enrolled participants, all comprising the ITT population	To provide further clarifications of the existing text
9.4.1 Efficacy Analyses	Added transfusion independence as an endpoint; clarified presentation of response rate results	To add relevant endpoint for AML studies
9.4.2 Safety Analyses	Removed paragraph on vital signs; modified text regarding physical examination to state that clinically significant abnormal examination findings would be reported as adverse events	To provide correct description of activities
10.2 Appendix 2: Clinical Laboratory Tests	Added hepatitis B virus antibody to examples of serology tests	To provide clarity

Section number and Name	Description of Change	Brief Rationale
10.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Added NCI-CTCAE v5.0 severity criteria	To provide details for investigator assessment of adverse events
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	To provide clarity

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

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_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Clay Smith, MD

Institution: OncoVerity, Inc

Signature: _____ Date: 6/21/23

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.