Janssen Research & Development*

Clinical Protocol

A Randomized Phase 2/3 Study of DACOGEN® (Decitabine) Plus Talacotuzumab (JNJ-56022473; Anti-CD123) Versus DACOGEN (Decitabine) Alone in Patients with AML who are not Candidates for Intensive Chemotherapy

Protocol 56022473AML2002; Phase 2/3

Amendment 7

Talacotuzumab (JNJ-56022473)

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

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Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	06 April 2015
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Amendment 4	29 March 2017
Amendment 5	26 April 2017
Amendment 6	02 August 2017
Amendment 7	31 October 2017

Amendments below are listed beginning with the most recent amendment.

Amendment 7 (31 October 2017)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: To further clarify the end of the study, as the end of study data collection to permit subjects who are deriving benefit from decitabine treatment to continue to receive decitabine after the end of study data collection.

Applicable Section(s)	Description of Change(s)
Rationale: To further clarify the end of the study, as the end of study data collection and to limit the monitoring of subjects who continue to receive decitabine to serious adverse events only.	
Synopsis: Overview of Study Design; Section 3.1 Overview of Study Design; Section 9.1.4 Follow-up Phase; Section 10.1 Completion; Section 14.5 Drug Accountability; Section 17.9.1 Study Completion/ End of Study	Changed “end of study” to “end of study data collection”. Clarified that for subjects who are continuing to derive benefit from decitabine treatment and are continuing to receive decitabine, only serious adverse events will be monitored and entered into the Company safety repository.
Rationale: To limit monitoring of subjects who continue to receive decitabine to serious adverse events only.	

Applicable Section(s)	Description of Change(s)
Synopsis: Efficacy Evaluations, Safety Evaluations; Time and Events Schedules 1C and 1D; Section 6.1 Dosing Schedule; Section 8 Prestudy and Concomitant Therapy; Section 9 Study Evaluations; Section 9.9 Safety Evaluations; Section 12.3 Procedures; Section 16.1 Study-Specific Design Considerations	Modified Time and Events Schedules; Clarified that for subjects who are continuing to derive benefit from decitabine treatment and are continuing to receive decitabine, only serious adverse events will be monitored and entered into the Company safety repository
Section 6.2.3 Decitabine Dose Modifications	Deleted sentence requiring consultation with Sponsor to resume decitabine treatment following a 28-day dose delay
Section 7 Treatment Compliance	Added statement that eCRFs will be closed

Amendment 6 (02 August 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: This amendment is based on Independent Data Monitoring Committee (IDMC) recommendation after results from the second interim analysis (final analysis for response endpoints and first analysis for overall survival [OS]) were reviewed. The IDMC recommended to close study enrollment and stop talacotuzumab treatment due to lack of efficacy in the talacotuzumab arm. Subjects in the combination arm should stop treatment of with talacotuzumab and can continue to receive DACOGEN only, in accordance with Principal Investigator decision and subject agreement.

Applicable Section(s)	Description of Change(s)
Rationale: Study conduct was changed due to IDMC recommendation after review of results from the second interim analysis.	
Synopsis: Overview of Study Design Part B; Section 3.1: Overview of Study Design; Section 3.2: Study Design Rationale; Section 5: Treatment Allocation and Blinding; Section 6.1.2 Part B; Section 16.1: Study-Specific Design Considerations	Enrollment in the study was closed; Subjects receiving talacotuzumab should discontinue talacotuzumab treatment and may continue decitabine treatment according to Principal Investigator decision and subject agreement.
Rationale: Data collection for ongoing subjects was changed due to changes in study conduct.	

Applicable Section(s)	Description of Change(s)
Synopsis: Overview of Study Design Part B, Efficacy Evaluations, Safety Evaluations; Time and Events Schedules 1B, 1C, and 2B; Section 3.1: Overview of Study Design; Section 3.2: Study Design Rationale; Section 9.1.1 Overview; Section 9.1.3 Open-label Treatment Phase; Section 9.1.4: Follow-up Phase; Section 9.2.1 Evaluations; Section 9.5.2 Assessment of CD123 Expression; Section 9.9 Safety Evaluations; Section 12.3: Procedures; Section 16.1: Study-Specific Design Considerations;	Added Time and Events Schedule 1C: all subjects will continue to be followed for survival and subsequent anti-cancer therapy. Subjects during the treatment phase with decitabine will be monitored for serious adverse events.
Rationale: End of study definition and time of final OS analysis was changed due to changes in study conduct.	
Synopsis: Overview of Study Design, Statistical Methods; Section 3.1: Overview of Study Design; Section 9.1.4: Follow-up Phase; Section 9.1.5: Disease Evaluation and Clinical Cut-off; Section 10.1: Completion; Section 17.9.1 Study Completion/ End of Study	Changed definition of end of study to 270 deaths or 6 months after the last subject was enrolled, whichever comes first; Changed time of final OS analysis to 270 deaths or 6 months after the last subject was enrolled, whichever comes first.

Amendment 5 (26 April 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: This amendment specifies enhanced precautionary measures to mitigate infusion-related reactions for subjects receiving talacotuzumab infusion.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify procedures during talacotuzumab infusion to reduce the incidence of infusion-related reactions	
Section 6.3.1 Preparation and Administration of Talacotuzumab	Changed infusion-rate guidance to slow initial infusion rate to 10 mL/hr with a maximum rate of 60 mL/hr for the first 4 cycles
Rationale: To add premedications for talacotuzumab infusion to reduce the incidence of infusion-related reactions	

Applicable Section(s)	Description of Change(s)
Synopsis: Dosage and Administration; Section 6.3.2 Talacotuzumab: Premedications	Amended dexamethasone 8 mg from 12 hours prior to infusion to BID approximately 2 days prior to infusion and approximately 3 hours prior to infusion. Added cimetidine
Rationale: To change maximum infusion rates after occurrence of an infusion-related reaction	
Section 6.3.4.1 Guidelines for the Interruption of Talacotuzumab Infusion due to Infusion-Related Reaction	Changed the maximum infusion rates following infusion-related reaction to 60 mL/hr for Cycles 1 to 4 and 150 ml/hr for subsequent cycles
Rationale: To increase the maximum volume of blood collected for subjects in the Talacotuzumab + DACOGEN arm to account for cytokine sampling	
Section 9.1.1 Overview	Increased maximum blood volumes for samples from subjects in the DACOGEN plus Talacotuzumab arm
Rationale: To add samples for cytokine analysis to investigate the mechanism of IRRs	
Time and Events Schedule 2B; Section 9.5.5 Cytokine Analysis (new section)	Added blood sampling for cytokine analysis

Amendment 4 (29 March 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: This amendment specifies new guidance for patient monitoring and availability of resuscitation equipment during talacotuzumab infusion.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify procedures during talacotuzumab infusion	
Section 6.3.1 Preparation and Administration of Talacotuzumab	Added clarification for patient monitoring during talacotuzumab infusion and availability of resuscitation equipment due to the occurrence of a fatal event of infusion-related reaction during talacotuzumab infusion; changed infusion-rate guidance and increased monitoring from 30 minutes to 1 hour after completion of infusion
Rationale: To continue ECG monitoring though no safety signal is seen	
Time and Events Schedule 1B; Section 9.9 Safety Evaluations	Removed language to stop ECG monitoring if no safety signal is seen
Rationale: To clarify biomarker and cytogenetic testing of bone marrow samples	
Time and Events Schedule 1B	Added language to clarify biomarker and cytogenetic testing to be performed per local standard of care at screening, suspected CR/CRi, and every disease assessment until, relapse or EOT

Amendment 3 (14 October 2016)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: This amendment specifies additional required premedication prior to talacotuzumab infusion in order to reduce the risk and severity of infusion-related reactions.

Applicable Section(s)	Description of Change(s)
Rationale: To reduce the risk and severity of infusion-related reactions.	
Synopsis; Section 6.3.2 Talacotuzumab: Premedication; Section 16.1 Study Specific Design Considerations	Added dexamethasone, montelukast, and specified diphenhydramine as premedications prior to infusion of talacotuzumab; clarified premedication procedures
Rationale: To change the name of JNJ-56022473 to talacotuzumab	
Throughout the protocol	Changed name of JNJ-56022473 to talacotuzumab
Rationale: To clarify when disease evaluations are performed	
Time and Events Schedule 1B	Changed disease evaluation from “at the end of each cycle” to every 2 cycles between Day 14 and Day 28 and at time of suspected CR /CRi and at time of suspected treatment failure or relapse from CR/CRi.
Rationale: To provide clarity for biomarker sampling	
Time and Events Schedules 1B and 2B	Clarified table for biomarker sampling
Rationale: To correct reasoning for leukopheresis and hydroxyurea treatment	
Section 4.1 Inclusion Criteria #3	Changed wording from “leukopheresis or hydroxyurea is permitted to decrease blast count” to “permitted to decrease WBC count”
Rationale: To clarify that prior systemic therapies for MDS or MPN are collected at screening	
Section 8: Prestudy and Concomitant Therapies	Added language that prior therapies for MDS and MPN should be collected during screening
Rationale: To align with previous amendment changing inclusion criterion 1	
Section 4.2: Exclusion Criteria; Attachments	Deleted “New York Heart Association class 3 or 4 congestive heart failure scale” from exclusion criteria to align with inclusion criterion 1; Deleted Attachment 3
Rationale: To correct definition of end of study	
Section 10.1 Completion; Section 17.9.1 Study Completion/ End of Study	Corrected definition of end of study to when 270 deaths have occurred or 6 months after the last subject is randomized, whichever occurs later.
Rationale: Minor errors were noted and corrected	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (28 June 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: This amendment was prepared in response to health authority review and clarifies inclusion criteria and the recommended dose of preinfusion medications prior to JNJ-56022473 administration.

Applicable Section(s)	Description of Change(s)
Rationale: To allow flexibility in scheduling due to patient / provider availabilities	
Time and Events Schedule 1B; Section 6.1.2 Part B	Added a ± 48 hour window (unless otherwise indicated) for Day 1 procedures For JNJ-56022473 administration window is ± 24 hours
Rationale: To provide clarity regarding sponsor oversight of subjects prior to inclusion	
Time and Events Schedule 1B	Added sponsor review of key eligibility data required prior to randomization
Rationale: To align with modifications that will be made to eligibility	
Time and Events Schedule 1B	Laboratory assessments for HBV surface antigen and hepatitis C antibodies removed and replaced by active hepatitis or history of HIV
Rationale: Bone marrow block no longer required at screening	
Time and Events Schedule 1B; Section 9.5.2 Assessment of CD123 Expression (part B)	Removed requirement for a bone marrow block at screening, and bone marrow aspirate/biopsy to be collected within 6 weeks of randomization; however, bone marrow samples are collected as indicated in the Time and Events schedule for central analysis
Rationale: To clarify the role of the IDMC and Sponsor in overall study decisions	
Synopsis Overview of Study Design Part B; Section 3.1 Overview of Study Design Part B	Clarified IDMC role and deleted wording that implied the IDMC was to decide upon study conduct; deleted repeated sentence in third paragraph
Rationale: To add objective per health authority feedback	
Synopsis, Secondary Objectives; Section 2.1.1 Objectives	Added rate of CR plus MRD negative CRi as an objective
Rationale: To add endpoint per health authority feedback	
Synopsis, Secondary Endpoints; Section 2.1.2 Endpoints; Section 11.4 Efficacy Analyses	Added rate of CR plus MRD negative CRi as an endpoint
Rationale: Added inclusion criteria to define subjects ineligible for intensive chemotherapy	
Synopsis Subject Population Part B; Section 4.1 Inclusion Criteria, Criterion 3.1	Added inclusion criteria to define subjects ineligible for intensive chemotherapy; aligned other criteria to agree with additions
Rationale: Aligned criteria to agree with added inclusion criteria	

Applicable Section(s)	Description of Change(s)
Section 4.2 Exclusion Criteria	Clarified criteria regarding other malignancies, removed chronic respiratory disease and LVEF <45% to align with modifications to inclusion criteria
Rationale: To define exclusion of subjects who have an active infection requiring treatment	
Section 4.2 Exclusion Criteria	Clarified criteria regarding infection
Rationale: There is no known hepatotoxicity or hepatitis reactivation with JNJ-56022473, so medical history of these conditions is acceptable for study entry	
Section 4.2 Exclusion Criteria	Exclusion criteria changed to active liver disease or hepatitis infection
Rationale: To agree with language and format of protocol template	
Section 4.3 Prohibitions and Restrictions	Added this section
Rationale: To increase monitoring and minimize the severity of infusion reactions	
Synopsis, Dosage and Administration; Section 6.3.1 Preparation and Administration of JNJ-56022473; Section 6.3.2 JNJ-56022473: Premedication Section 6.3.4.1 Guidelines for the Interruption of JNJ-56022473 Infusion due to Infusion-related Reactions	Clarified maximum rate of infusion and monitoring of subjects; Increased mandatory premedication to 100 mg methylprednisolone and clarified number of cycles for premedication;
Rationale: To clarify JNJ-56022473 dosing modifications	
Section 6.3.3 JNJ-56022473 Dosing Modifications	Clarified text regarding JNJ-56022473 dose delays
Rationale: To provide clarity for recommended supportive therapies	
Section 8.1 Permitted Medications and Supportive Therapies	Clarified wording regarding growth factor and anti-infective use
Rationale: To clarify that plasmapheresis must be discontinued prior to start of study therapy	
Section 8.2 Prohibited Therapies	Clarified that plasmapheresis must be discontinued prior to start of study therapy
Rationale: Corrected blood volumes collected during the study	
Section 9.1.1. Overview	Changed blood volumes to agree with section 16.1
Rationale: To provide the definition of end of study	
Section 9.1.4 Follow-up Phase	End of study was redefined as when 270 deaths have occurred or 6 months after the last subject is randomized
Rationale: To ensure discontinuation criteria defined in the protocol are met	

Applicable Section(s)	Description of Change(s)
Section 9.2.1.1 Disease Status; Section 10.2 Discontinuation of the Treatment Phase	Added text to ensure that criteria for discontinuation of subjects is reviewed by the Sponsor prior to discontinuation
Rationale: Proteomics evaluations s will not be performed	
Section 9.5.5 Proteomics Evaluation (Part B)	Deleted this section
Rationale: To align with modified eligibility criteria	
Section 9.9 Safety Evaluations	Removed HBsAg and hepatitis C virus antibody testing at screening
Rationale: To provide clarity and to document the level of sponsor oversight	
Section 10.2 Discontinuation of the Treatment Phase	Added text that all treatment discontinuations will be reviewed and approved by the Sponsor
Rationale: To conform to health authority feedback	
Synopsis, Statistical Methods, Section 11.2 Interim and Final Analyses	Clarified role of the IDMC. Modified text and statistical parameters for efficacy analyses
Rationale: To clarify the composition and role of the IDMC	
Section 11.12 Independent Data Monitoring Committee	Added text defining the IDMC and function of the IDMC
Rationale: To provide anticipated events	
Section 12.3.1 All Adverse Events; Attachment 4	Added language regarding anticipated adverse events
Rationale: To provide reference for suitable bloods volumes withdrawn during the study	
Section 16.1 Study-specific Design Considerations	Removed blood volumes withdrawn for the study; added reference for suitability of blood volume withdrawn
Rationale: Minor errors were noted and corrected	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The study was originally designed as a Phase 2 study with a total of 120 subjects and a primary endpoint of event-free survival (EFS). An interim analysis with 45 EFS events was planned in the original study to determine if the study would be continued toward the end with 120 subjects. This amendment changes the primary endpoint of the study to 2 primary endpoints of complete response (CR) rate and overall survival (OS) and up to 400 subjects enrolled. An interim analysis is included in the amended protocol after 80 subjects have been randomized (approximately 40 subjects per arm) and followed for 4 months. The results of this interim analysis will provide guidance for a decision to continue enrollment to 400 subjects or stop enrollment.

Applicable Section(s)	Description of Change(s)
Rationale: To emphasize study endpoints	
Synopsis Objectives, Endpoints and Hypothesis; Section 2.1 Objectives and Endpoints	Moved subsection that defined study endpoints
Rationale: To advance development of JNJ-56022473	
Synopsis Objectives and Endpoints; Section 2.1 Objectives and Endpoints; Section 9.5.3 Minimal; Residual Disease Assessment (Part B)	Changed primary and secondary objectives and endpoints for Part B of the study; Added minimal residual disease evaluation as a secondary endpoint
Rationale: To change the hypothesis based on changes in primary objectives	
Synopsis Hypothesis; Section 2.2 Hypothesis	Changed the hypothesis to reflect complete response rate and overall survival as primary objectives
Rationale: To change the timing of and agent used for premedication for subjects who receive JNJ-56022473	
Synopsis Dosage and Administration; Section 6.3.2 JNJ-56022473 Premedication; Section 16.1 Study Specific Design Considerations	The use of hydrocortisone as a premedication agent was switched to methylprednisolone for the first 2 cycles of JNJ-56022473 treatment
Rationale: To change the study design to permit accelerated development of JNJ-56022473 if predefined statistical criteria are met	
Synopsis Overview of Study Design; Section 3.1 Overview of Study Design; Section 11.2 Interim and Final Analyses	Added details of a revised design to continue Part B; limited Study Evaluation Team evaluations to Part A; Added Independent Data Monitoring Committee participation in Part B; Added independent central review of efficacy
Rationale: It can take 2 to 4 weeks for cytogenetic results. Newly diagnosed patients cannot wait this long to begin treatment for acute myeloid leukemia (AML). The remaining stratification factors (Eastern Cooperative Oncology group [ECOG] performance status score and primary vs secondary AML) adequately account for factors that influence outcomes in patients with AML.	

Applicable Section(s)	Description of Change(s)
Synopsis Overview of Study Design; Section 3.1 Overview of Study Design; Section 3.2 Study Design Rationale; Section 5 Treatment Allocation and Blinding; Section 11.4 Efficacy Analyses	Removed cytogenetic (adverse vs other) as a stratification factor
Rationale: To describe interim and final analyses for Part B of the study	
Synopsis Statistical Methods; Section 11.2 Interim and Final Analyses	Described statistical decision making rules for Part B of the study
Rationale: To update Time and Events Schedule 1B based on investigator feedback and consistency with rest of protocol	
Time and Events Schedule 1B; Section 9.9 Safety Evaluations	Expanded the window for pre-dosing assessments for each cycle from 48 hours to 3 days; added Medical Resource Utilization determination as a procedure under Safety Assessments; added peripheral blast counts to Hematology Laboratory Assessments; clarified that the diagnostic bone marrow block required at screening may be from a historic sample; added a procedure that defines disease evaluation under Disease Evaluations; changed frequency of Day 1 bone marrow assessments from Cycle 4 to every second cycle starting at Cycle 2.
Rationale: To expand cardiac testing of subjects	
Time and Events Schedule 1B; Section 9.9 Safety Evaluations	Added LVEF determination at end-of-treatment; Added ECG monitoring during the study for both treatment arms and at end-of-treatment.
Rationale: To clarify criteria and measurement of LVEF	
Time and Events Schedule 1A and 1B; Section 4.2 Exclusion Criteria	Added LVEF determination as clinically indicated during the study to the Time and Events Schedule for consistency with Section 9.9; revised exclusion criterion #12 so that only LVEF<45% is excluded
Rationale: To clarify Adverse event information collected during the follow-up phase	
Time and Events Schedule 1A and 1B, Section 9.9 Safety Evaluations, Section 12.3.1 All Adverse Events	Drug-related ≥ Grade 3 adverse events and drug-related serious adverse events will be followed until resolution during the follow-up phase
Rationale: To clarify source documentation for eligibility criteria	
Time and Events Schedules 1A and 1B	Added note regarding source documentation and to assess the clinical status of the subject again prior to the first dose of study drug
Rationale: To Clarify Disease Evaluations to include clinical presentation	

Applicable Section(s)	Description of Change(s)
Synopsis Efficacy Evaluations; Time and Events Schedule 1B; Section 3.1 Overview of Study Design; Section 9.2.1 Efficacy Evaluations	Added clinical presentation to disease assessments evaluated for efficacy; clarified details for bone marrow biopsy/aspirate
Rationale: To update Time and Events Schedule 2B to remove unneeded pharmacokinetic (PK) and biomarker samples	
Time and Events Schedule 2B; Section 9.5.4 Immunophenotyping (Part B)	Removed the JNJ-56022473 PK sample on Day 1 Cycle 4; limited PK sampling after 120 subjects have enrolled; removed samples for testing NK cell directed ADCC and T-cell mediated cytotoxicity assay
Rationale: To update safety information for CSL362	
Section 1.2 CSL362 Phase 1 Experience	Updated safety information with a clinical cut-off date of 28 January 2015
Rationale: To change the rationale to accommodate the change in primary objectives and endpoints	
Section 3.2 Study Design Rationale	Changed rationale for primary endpoints
Rationale: To Provide a statement that waivers to eligibility criteria are not allowed	
Section 4 Subject Population	Added statement: Waivers are not allowed.
Rationale: To clarify inclusion criteria for blood cell counts	
Section 4.1 Inclusion Criteria	Clarified that the platelet count of $\geq 10 \times 10^9$/L was with or without transfusion; defined the white blood cell count criteria as $\leq 40 \times 10^9$/L
Rationale: To Expand the exception to exclusion criterion to include patients with myelofibrosis	
Section 4.2 Exclusion Criteria	Deleted repetitive criterion of Hepatitis B or C virus positivity
Rationale: To clarify treatment discontinuation for Part B	
Section 6.12 Part B; Section 6.23 Decitabine Dose Modifications; Section 6.33 JNJ-56022473 Dose Modifications; Section 9.1.3 Open-Label Treatment Phase; Section 10.2 Discontinuation of the Treatment Phase	Clarified that subjects in Arm 1 (Part B) could discontinue 1 drug treatment and continue treatment with the other agent
Rationale: To Extend the maximum delay of decitabine dosing to 28 days	
Section 6.2.3 Decitabine Dose Modifications	Changed the maximum delay for decitabine treatment to 28 days from 14 days
Rationale: To further define the administration of JNJ-56022473 to minimize infusion-related reactions	

Applicable Section(s)	Description of Change(s)
Section 6.3.1 Preparation and Administration of JNJ-56022473	Clarified that JNJ-56022473 dosing is based on the weight of the subject at the Day 1 Assessment of each cycle; Clarified that the volume of infusion is 250 mL; Defined the infusion rates for JNJ-56022473
Rationale: To Change requirements for dose modifications due to Grade 4 hematological toxicity based upon investigator feedback	
Section 6.3.3 JNJ-56022473 Dosing Modifications	Changed the requirement for dose delays of JNJ-56022473 due to hematological toxicity from not responsive to supportive care to per investigator judgment
Rationale: To Clarify the clinical management of infusion-related reactions and JNJ-56022473 dose modifications due to infusion-related reactions	
Section 6.3.4 Management of Potential Hypersensitivity/ Infusion-related Reactions	Defined the recommended management of infusion-related reactions and modifications for JNJ-56022473 treatment
Rationale: To expand permitted medications for febrile neutropenia	
Section 8.1 Permitted Medications and Supportive Therapies	Added recommendations for growth factor use
Rationale: To allow vaccination with killed virus vaccines	
Section 8.2 Prohibited Therapies	Restricted prohibited therapies to live attenuated vaccination
Rationale: To describe clinical cutoffs in Part B of the study	
Section 9.1.5 Disease Evaluation and Clinical Cutoff	Added clinical cutoff in Part B of the study
Rationale: To define an Independent Data Monitoring Committee	
Section 11.12 Independent Data Monitoring Committee; Section 16.1 Study-Specific Design Considerations	Added details for a Data Monitoring Committee
Rationale: To modify sample size for revised study design	
Section 11.3 Sample Size Determination	Described operational characteristics for Part B of the study
Rationale: To describe statistical analyses for CR, OS primary endpoints	
Section 11.4 Efficacy Analyses	Described analyses for primary endpoints for Part B of the study
Rationale: To define immunogenicity results formats	
Section 11.5 Immunogenicity Analyses	Added description of immunogenicity analysis result formats
Rationale: Provide description of methods for adverse event detection	

Applicable Section(s)	Description of Change(s)
Section 12 Adverse Event Reporting	Added subsection of methods of detecting adverse events and serious adverse events
Rationale: To Provide an eSource system as an alternate data source for clinical data	
Section 17.4 Source Documentation	Defined the eSource system
Rationale: To clarify language regarding Case Report Form completion	
Section 17.5 Case Report Form Completion	Clarified language regarding Case Report Form completion
Rationale: Minor errors were noted and corrected	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Randomized Phase 2/3 Study of DACOGEN® (Decitabine) Plus Talacotuzumab (JNJ-56022473; Anti-CD123) Versus DACOGEN (Decitabine) Alone in Patients with Acute Myeloid Leukemia (AML) who are not Candidates for Intensive Chemotherapy

EudraCT NUMBER: 2015-011611-12

DACOGEN (decitabine) is a hypomethylating agent approved in the European Union and 21 other countries for the treatment of patients with AML who are over the age of 65 and who are not candidates for intensive chemotherapy. DACOGEN (decitabine) is also recommended in the National Comprehensive Cancer Network (NCCN) Guidelines in the USA for the treatment of patients with AML. For the purposes of this protocol the generic name decitabine will be used hereafter to refer to the agent to be used in this study.

Talacotuzumab, previously known as JNJ-56022473 or CSL-362, is a fully humanized monoclonal IgG1 antibody directed against the α-subunit of the interleukin-3 (IL-3) receptor also known as the CD123 antigen.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

OBJECTIVES

Primary Objectives

Part A

The primary objectives of Part A of the study are to assess safety and to confirm the recommended Phase 2 dose (RP2D) of talacotuzumab monotherapy.

Part B

The primary objectives of Part B of the study are to assess complete response (CR) rate and overall survival (OS) in patients with previously untreated AML who are not eligible for intense induction chemotherapy and who are randomly assigned to receive decitabine plus talacotuzumab at the RP2D or decitabine alone.

Secondary Objectives

Part B

The secondary objectives are to assess the event-free survival (EFS), the overall response rate (ORR, defined as the rate of CR + complete response with incomplete blood count recovery [CRi]), the rate of CR plus MRD negative CRi, relapse-free survival (RFS), time to and duration of response, and the safety profile of study treatments; to assess the pharmacokinetics (PK) of decitabine and talacotuzumab when used alone or in combination; to assess the immunogenicity of talacotuzumab in combination with decitabine, to evaluate minimal residual disease (MRD) and to evaluate patient-reported outcomes measures (PRO) using the FACT LEU and EQ-5D-5L instruments.

ENDPOINTS

Part A

- To assess safety and determine dose-limiting toxicities (DLTs)

Part B

2 Primary Endpoints (Part B)

- CR rate
- Overall survival (OS)

Secondary Endpoints (Part B)

- EFS, defined as the time from randomization to treatment failure, relapse from CR/CRi, or death from any cause, whichever occurs first. Treatment failure is defined as >25% absolute increase in the bone marrow blast count from baseline to the present assessment.
- ORR (CR + CRi);
- Rate of CR plus MRD negative CRi;
- Time to response, defined for subjects who achieved best response of CR or CRi as time from randomization to achieving the best response;
- Duration of response, defined for subjects who achieved best response of CR or CRi as time from achieving CR or CRi to relapse;
- Relapse-free survival (RFS) defined for subjects who achieved CR or CRi as the time from achieving CR or CRi to disease relapse or death from any cause;
- Safety profile;
- Pharmacokinetics;
- Immunogenicity;
- MRD;
- Patient-reported outcomes (PROs) using the FACT-Leu and EQ 5D 5L.

Exploratory Endpoints (Part B)

- Pharmacokinetic/pharmacodynamic relationships associated with biomarkers, pharmacodynamic (PD) markers and clinical end points;
- To explore biomarkers associated with clinical response;
- Medical resource utilization.

Hypothesis

In patients with untreated AML who are not eligible for intense induction chemotherapy it is hypothesized that treatment with a combination regimen of decitabine and talacotuzumab as compared with decitabine alone will improve the CR rate or extend survival or both.

OVERVIEW OF STUDY DESIGN

Part A

This is an open label, multicenter study; in Part A, the RP2D of talacotuzumab monotherapy will be confirmed in subjects with AML for whom experimental therapy is appropriate (as assessed by their treating physician). Part A will include approximately 6 subjects to assess the clinical safety and pharmacokinetics/pharmacodynamics (PK/PD) of talacotuzumab as part of the comparability testing package for talacotuzumab, a monoclonal antibody with the same amino acid sequence as CSL362, but produced in a different cell line with a different process. A prior Phase 1 study of CSL362 assessed the safety and PK profile and established the RP2D as 9 mg/kg. Comparability testing of talacotuzumab and CSL362 has shown the antibodies to behave similarly in biophysical, biochemical, and preclinical assessments. Pharmacodynamic studies in cynomolgus monkeys showed similar levels of biological activity between CSL362 and talacotuzumab (ie, basophil and plasmacytoid dendritic cell [pDC] depletion; natural killer [NK] cell number and activity). Additionally, the PK profiles of talacotuzumab following 30 and 100 mg/kg IV dosing of cynomolgus monkeys are highly similar to those of CSL362. Following the first weekly IV dose, mean C_{max} and $AUC_{0\text{-}167h}$ of talacotuzumab are 91% and 94% of those observed for CSL362, respectively. Further detail regarding preclinical studies of CSL362 and talacotuzumab is provided in the JNJ-56022473 Investigator's Brochure.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. During Part A, the safety, PK, and PD of talacotuzumab will be assessed. After 1 dose of single-agent talacotuzumab and a 14-day post-dose assessment period, subjects will be assessed for safety to confirm the RP2D and will then start subsequent cycles of combination therapy of decitabine + talacotuzumab using the same dosing schedule described for Part B.

Part B

In Part B, subjects with AML who are not candidates for intensive chemotherapy will be assigned randomly in a 1:1 ratio to receive decitabine + talacotuzumab (Arm 1) or decitabine alone (Arm 2). Approximately 400 subjects will be enrolled in Part B.

Part B of the study will begin after the RP2D of talacotuzumab is confirmed in Part A. Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0-1 versus 2) and type of AML (de novo versus secondary). Subjects in both treatment arms will receive decitabine (20 mg/m^2 per day) on Days 1 to 5 of each 28-day cycle. For subjects randomized to the decitabine + talacotuzumab arm, talacotuzumab will be administered intravenously (IV) at the RP2D determined in Part A on Day 8 and Day 22 every 28 days. Treatment is continued until treatment failure, relapse from CR or CRi, unacceptable toxicity, or death.

Part B is designed to be a seamless Phase 2/3 study with 2 primary endpoints, CR rate and OS. The study will have 3 interim analyses. The first interim analysis will occur after approximately 80 subjects (40 subjects per arm) have been randomized and followed for at least 4 months. Guided by predefined statistical criteria based on CR and CR+CRi the study will continue enrollment to the prespecified Phase 3 sample size of 400 subjects or discontinues enrollment. Approximately 120 subjects are expected to have been randomized by the time the outcome of the interim analysis is available; this is the estimated Phase 2 sample size. No changes in design elements are planned based on this interim analysis.

If the enrollment continues to 400 subjects (approximately 200 subjects per arm), the pre-specified design elements are:

- A second interim analysis occurs after approximately 160 subjects (approximately 80 subjects per arm) have been randomized and followed for at least 4 months; this is the final analysis for CR and the first interim analysis for OS. The study will not be stopped on the basis of the CR results;
- A third interim analysis (ie, the second interim analysis of OS) will be conducted when 180 deaths have occurred;
- The final analysis of OS will take place when 270 deaths have occurred or 6 months after the last subject was enrolled whichever occurs first.

If the study stops enrollment at the first interim analysis, it is expected that approximately 120 subjects will have been randomized. These subjects will continue to be followed. The clinical cut-off in this case will be when the pre-specified 90 EFS events have occurred.

Safety reviews will be performed in Part A and Part B. The safety assessments in Part A will occur prior to the initiation of Part B. This will include safety and available PK and PD data from single-agent talacotuzumab and the preliminary safety of the combination of decitabine + talacotuzumab. A Study Evaluation Team (SET) will monitor safety and study conduct on an ongoing basis during Part A of the study.

An Independent Data Monitoring Committee (IDMC) will be established to evaluate safety and efficacy data collected during Part B of the study as described in Section 3.1.

In addition to evaluations by investigators, disease status will be reviewed and determined by independent central review in a blinded fashion. Disease status based on independent central review will be the primary source for efficacy analyses.

After review of the data from Interim Analysis #2, the IDMC informed the Sponsor that the futility criterion for OS was met and that the CR rate did not meet per-protocol defined statistical significance. Given the lack of efficacy advantage of talacotuzumab + decitabine versus decitabine alone, the incidence of infusion-related reactions, and the complexities with premedications for drug administration, the benefit/ risk ratio is not favorable to continue treatment with talacotuzumab. The IDMC recommended closure of enrollment to the study and that subjects receiving talacotuzumab + decitabine should discontinue talacotuzumab treatment and may continue decitabine alone, according to Principal Investigator decision and subject agreement. All subjects will continue to be followed for survival and subsequent anti-cancer therapy. During the treatment phase with decitabine, subjects will be monitored for serious adverse events.

The end of study data collection is defined as when 270 deaths have occurred or 6 months after the last subject is enrolled, whichever occurs first. At that time, follow up of subjects will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository as described under Amendment 7.

SUBJECT POPULATION

Part A

Key eligibility criteria include the following: subjects diagnosed with AML according to the World Health Organization (WHO) 2008 classification system fulfilling all of the following criteria:

- Patients with AML (treatment naive or relapsed) for whom experimental therapy is appropriate as assessed by their treating physician; subjects should not have had prior treatment with a hypomethylating agent;

- White blood cell (WBC) count ≤ 40 X 10^9/L.

Part B

Key eligibility criteria include the following: subjects who are:

- Age ≥75 years old
- Age ≥65 up to 75 and have at least 1 of the following:

  1. Congestive heart failure or ejection fraction ≤50%
  2. Creatinine >2 mg/dL, dialysis or prior renal transplant
  3. Documented pulmonary disease with lung diffusing capacity for carbon monoxide (DLCO) ≤65% of expected, or forced expiratory volume in 1 second (FEV1) ≤65% of expected or dyspnea at rest requiring oxygen
  4. ECOG performance status of 2
  5. Prior or current malignancy that does not require concurrent treatment
  6. Unresolved infection
  7. Comorbidity that, in the Investigator's opinion, makes the patient unsuitable for intensive chemotherapy which must be documented and approved by the Sponsor before randomization

- De novo or secondary AML according to the World Health Organization (WHO) 2008 classification; (post myelodysplastic syndrome [MDS] or myeloproliferative neoplasm [MPN] or after leukemogenic chemotherapy),
- Previously untreated AML (except emergency leukopheresis and/or hydroxyurea during the screening phase to control hyperleukocytosis but must be discontinued at least one day prior to start of study therapy;
- Not eligible for an allogeneic hematopoietic stem cell transplantation,
- Eastern Cooperative Oncology Group (ECOG) Performance Status score of ≤ 2

DOSAGE AND ADMINISTRATION

Part A

In Part A, 6 subjects will receive 1 dose of talacotuzumab at 9 mg/kg on Day 1 as a 180-minute IV infusion. Dose-limiting toxicities (DLTs) will be assessed during the DLT evaluation period which is Cycle 1 (14 days). If no DLTs are observed or are observed in 1 of the 6 subjects, the dose of 9 mg/kg talacotuzumab may be established as the RP2D by the SET. If DLTs are observed in ≥2 of the 6 subjects, Part A may continue with additional enrollment of 3 to 6 subjects at a lower dose level of talacotuzumab to be determined by the SET. All subjects will receive premedication with hydrocortisone or equivalent IV steroid to prevent infusion reactions. After completion of Cycle 1, all subjects in Part A will then start subsequent cycles of combination therapy of decitabine + talacotuzumab.

Part B

In Part B of the study, subjects in the decitabine plus talacotuzumab arm will receive talacotuzumab IV at the RP2D over approximately 180 minutes. Talacotuzumab will be administered on Days 8 and 22. Decitabine will be administered at 20 mg/m^2 as a 1-hour IV infusion for 5 consecutive days (Days 1 to 5) every 28 days (1 treatment cycle) to subjects in both treatment arms. During the first 4 treatment cycles, all subjects in the decitabine + talacotuzumab arm must receive premedication with dexamethasone, methylprednisolone, acetaminophen (paracetomol), cimetidine, diphenhydramine, and montelukast prior to talacotuzumab dosing to prevent infusion-related reactions. If no infusion-related reactions are seen for

2 consecutive cycles during the first 4 cycles, then premedication may be modified by the investigator after discussion with the Sponsor for Cycle 5 and subsequent talacotuzumab treatments. In the event an infusion-related reaction (independent of severity) occurs in Cycle 5 and subsequent talacotuzumab treatments, premedications need to be reintroduced.

Subjects in the decitabine only arm will receive the 5-Day decitabine dosing regimen (20 mg/m^2 as a 1-hour IV infusion for 5 consecutive days every 28 days) alone.

EFFICACY EVALUATIONS

Disease evaluations will include peripheral blood assessments, bone marrow assessments, and clinical presentation. Disease status will be evaluated according to Response Criteria in AML with modifications for treatment failure. Survival status and subsequent anticancer therapy will also be collected. Blood samples will also be collected to assess pharmacokinetics, immunogenicity, pharmacodynamics, MRD, and biomarkers.

Following Amendment 6, which incorporated the IDMC's recommendations to close enrollment to the study and discontinue talacotuzumab treatment for subjects receiving talacotuzumab + decitabine and offer to continue decitabine alone, all subjects will continue to be followed for survival and subsequent anti-cancer therapy. During the treatment phase with decitabine, subjects will be monitored for serious adverse events.

Following Amendment 7 and when 270 deaths have occurred or 6 months after the last subject is enrolled (whichever occurs first), follow up of subjects and data collection will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository.

SAFETY EVALUATIONS

Safety evaluations will include adverse event monitoring, vital signs measurements, physical examinations, electrocardiograms, clinical laboratory parameters (hematology and chemistry), and ECOG performance status. Other malignancies will also be recorded.

In addition, a safety review by the IDMC of the accumulative data will be performed when approximately 20 subjects (10 subjects from each arm) have been enrolled in Part B and followed for at least 1 month to assess the safety and tolerability of the combination treatment. This review will also include all safety, PK, and PD data available from Part A.

Following Amendment 6, which incorporated the IDMC's recommendations to close enrollment to the study and discontinue talacotuzumab treatment for subjects receiving talacotuzumab + decitabine and offer to continue decitabine alone, all subjects will continue to be followed for survival and subsequent anti-cancer therapy. During the treatment phase with decitabine, subjects will be monitored for serious adverse events.

Following Amendment 7 and when 270 deaths have occurred or 6 months after the last subject is enrolled (whichever occurs first), follow up of subjects and data collection will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository.

STATISTICAL METHODS

Approximately 6 subjects will be enrolled in Part A of the study in order to confirm the recommended dose of talacotuzumab for Part B. The SET consisting of selected investigators, sponsor medical monitors, the sponsor's statistician, and the sponsor's clinical pharmacologist, will review all available

data upon completion of the 14-day period following 9 mg/kg talacotuzumab treatment (Cycle 1) to determine DLTs, if the dose is acceptable, and subsequently, will confirm the RP2D. If no DLTs are observed or are observed for 1 of the 6 subjects, the dose of 9 mg/kg talacotuzumab may be established as the RP2D by the SET. If DLTs are observed in ≥2 of the 6 subjects, Part A may continue with additional enrollment of 3 to 6 subjects at a lower dose level of talacotuzumab to be determined by the SET. Additionally, the SET will review accumulated safety data from Part A prior to the initiation of Part B.

Part B of the study includes an interim analysis based on response rates of CR and CR+CRi that will occur after approximately 80 subjects (40 subjects per arm) have been randomized and followed for at least 4 months. The results of this interim analysis will be used to guide if the study continues enrollment to the prespecified 400 subjects or stops enrollment. Enrollment will continue during the interim analysis; it is estimated that approximately 120 subjects will have been randomized by the time the results of the first interim analysis are available.

The statistical criteria to guide the decision making will be based on the difference (Δ) in response rate between the 2 treatment arms (decitabine + talacotuzumab minus decitabine alone) as the following:

- If ΔCR ≥15% or Δ(CR+CRi) ≥25%, then the study may continue enrollment to 400 subjects
- If ΔCR <15% and Δ(CR+CRi) <25%, then the study may stop enrollment at approximately 120 subjects

Event-free survival and all available safety, PK, PD, MRD, and biomarker data will also be reviewed at the time of this interim analysis. The final decision to continue enrollment will be based on the totality of the data and other development considerations.

If the study continues enrollment to 400 subjects, then the overall Type 1 error of 0.05 (2-sided) will be allocated between the primary endpoints of CR rate and OS using a gate-keeping procedure as described below:

- There will be a formal statistical testing for superiority for CR at the interim analysis of 80 subjects with 2-sided α=0.001. The final analysis of CR (in terms of formal statistical hypothesis testing) will take place 4 months after 160 subjects have been randomized (to occur at the same time as the first interim analysis of OS) with 2-sided α=0.009. The study and collection of response data continue after the final CR analysis regardless of the outcome of the analysis.
- Overall 2-sided α=0.04 for OS; and if the final analysis of CR achieves statistical significance, then α=0.009 allocated to CR can be reclaimed by the OS analysis, ie, OS can be tested at the overall level of 0.049.
- The 2 interim analyses and final analysis for OS will utilize the O'Brien-Fleming α-spending procedure.

If the study continues enrollment to 400 subjects, a clinical cut-off will be when 270 deaths have occurred. If the study stops enrollment after the first interim analysis, the clinical cut-off will be when 90 EFS events have occurred. Enrollment was terminated after Interim Analysis #2 and the study will end 6 months after the last subject was enrolled.

Statistical details of the interim analysis, decision guidance, and study conduct are provided in Section 11.2.

TIME AND EVENTS SCHEDULE – TABLE 1A [PART A]

Procedure (Part A)	Notes	Screening Phase	Open-Label Treatment Phase			Follow-up Phase
		Within 28 days before Day 1	Cycle 1 (14 days)	Day 1 of each subsequent cycle (28 days) unless otherwise noted	EOT	Every 3 months (±7 days)
NOTE: **The EOT Visit** should occur within 30 days (±7 days) of last dose for subjects. **The Follow-up Phase** will continue until death, loss to follow-up, consent withdrawal for study participation, or study end, whichever occurs first.						
Screening/Administrative						
Informed consent	ICF must be signed before any study-related procedures	X				
Demography/medical history		X				
Eligibility criteria	Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4, Source Documentation. Check clinical status again before first dose of study medication.	X				
Study Drug Administration (for details see also Section 6)						
Decitabine				Days 1, 2, 3, 4 and 5		
Talacotuzumab			Day 1	Days 8 and 22		
Safety Assessments						
Physical examination	Must be assessed within 48 hrs of Day 1 of each specified cycle, reviewed prior to starting the cycle and changes that are clinically significant must be reported on the AE page	X	X	X	X	
ECOG performance status evaluation	Must be assessed within 48 hrs of Day 1 of each specified cycle	X	X	X	X	

Procedure (Part A)	Notes	Screening Phase	Open-Label Treatment Phase			Follow-up Phase
		Within 28 days before Day 1	Cycle 1 (14 days)	Day 1 of each subsequent cycle (28 days) unless otherwise noted	EOT	Every 3 months (±7 days)
Vital signs	Temperature, blood pressure (BP) and heart rate (HR) will be assessed prior to each study treatment dosing; On talacotuzumab dosing days BP/HR are measured pre-dose and every 15 min during the first 90 min, and then at 30-min intervals for the remainder of the infusion. For the first infusion, also every 30 min. post-infusion up to 1.5 hr after the infusion; as clinically indicated.	X	X	X	X	
Weight	Must be assessed prior to dosing on Day 1 of each specified cycle, in case of weight loss of >10% within a cycle, the dose of study drug must be recalculated	X	X	X	X	
Height		X				
LVEF	MUGA scan is preferred. Echocardiogram can be used if MUGA is not available.	X	as clinically indicated			
ECG	QTcF will be assessed at the time of screening. If QTcF is >470 msec, repeat ECG 2 additional times approximately 3 – 5 minutes apart. Average the QTcF of all 3 ECGs to determine if the subject meets the QTc eligibility criteria	X	Only if clinically indicated			
Concomitant medications	See Section 8 for detailed instructions; includes transfusion requirements	Continuous from the time of signing of ICF until 30 days after last study drug dose				Concomitant medications for related AEs of Grade ≥3 and SAEs regardless of relationship only; subsequent anticancer therapy

Procedure (Part A)	Notes	Screening Phase	Open-Label Treatment Phase			Follow-up Phase
		Within 28 days before Day 1	Cycle 1 (14 days)	Day 1 of each subsequent cycle (28 days) unless otherwise noted	EOT	Every 3 months (±7 days)
Adverse events	See Section 12 for detailed instructions.	Continuous from the time of signing of ICF until 30 days after last dose of last study drug				Related AEs of Grade ≥3 and related SAEs; follow until resolution
Patient-reported outcomes						
FACT-Leu	PROs should be performed on Day 1 of each cycle before dosing and before any study tests or procedures or consultations are conducted.		X	X	X	Only at first FU
EQ-5D-5L			X	X	X	Only at first FU
Laboratory Assessments						
Hematology	At least the following parameters (hemoglobin, platelet count, WBC, monocytes, basophils, eosinophils, absolute neutrophil count, absolute lymphocyte count, and peripheral blasts) must be assessed within 48 hrs of the indicated days of each cycle and results reviewed prior to dosing.	X	Day 1	Days 1, 8 and 22	X	
Coagulation panel	aPTT, INR or prothrombin time (PT) must be assessed at screening and as clinically indicated	X				
Clinical chemistry	At least the following parameters (AST, ALT, sodium, potassium, magnesium, BUN, phosphate, uric acid, calcium, alkaline phosphatase, creatinine, LDH, total bilirubin) must be assessed within 48 hrs of Day 1 of each cycle and results reviewed prior to starting the cycle.	X	X	X	X	
HBV surface antigen and hepatitis C (antibodies)		X				

Procedure (Part A)	Notes	Screening Phase	Open-Label Treatment Phase			Follow-up Phase
		Within 28 days before Day 1	Cycle 1 (14 days)	Day 1 of each subsequent cycle (28 days) unless otherwise noted	EOT	Every 3 months (±7 days)
Serum β-hCG or urine pregnancy test	For women of childbearing potential only	X	Only if clinically indicated			
Disease Evaluations: Every effort should be made to conduct disease evaluations as per schedule (window ±7 days). Refer to Section 9.2 for details on efficacy evaluations						
Bone marrow aspirate/biopsy	Bone marrow diagnostic block required at screening from historic sample	X				
	Disease status evaluation	X	At time of suspected treatment failure	At Cycle 5 (between Day 14 to 28) At time of suspected CR /CRi At time of suspected treatment failure or relapse from CR/CRi	X (unless done within 2 weeks)	
Imaging	Per local standard of care and as clinically indicated. Report the disease assessment for AML related abnormalities including all sites of extramedullary disease	X		Repeat as clinically indicated per local standards. If extramedullary disease at baseline, repeat imaging (using the same modality) at time of best response		
Survival, subsequent therapy, other malignancies						X

Procedure (Part A)	Notes	Screening Phase	Open-Label Treatment Phase			Follow-up Phase
		Within 28 days before Day 1	Cycle 1 (14 days)	Day 1 of each subsequent cycle (28 days) unless otherwise noted	EOT	Every 3 months (±7 days)
Pharmacokinetic, Pharmacodynamic, and Biomarker Assessments see TIME AND EVENTS SCHEDULE (PK AND BIOMARKERS) – TABLE 2A						

Abbreviations: AE=adverse event; ALT= alanine aminotransferase; AML=acute myeloid leukemia; AST= aspartate aminotransferase; β-hCG=beta human chorionic gonadotropin; BP=blood pressure; BUN= blood urea nitrogen; CR= complete response; CRi= complete response with incomplete blood cell count recovery; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; EQ=EuroQol; F/U= follow-up; HBV: hepatitis B virus; HR=heart rate; ICF=informed consent form; INR= international normalized ratio; LDH= lactate dehydrogenase; LVEF= left ventricular ejection fraction; MUGA= Multi Gated Acquisition Scan; NK= natural killer (cells); PD=pharmacodynamics(s); PK=pharmacokinetic(s); PRO= patient-reported outcomes; PT= prothrombin time; aPTT= partial thromboplastin time; SAE=serious adverse event; T&E=Time & Events; WBC= white blood cell.

TIME AND EVENTS SCHEDULE – TABLE 1B [PART B] UP TO AND INCLUDING AMENDMENT 5

Procedure (Part B)	Notes	Screening Phase	Open-Label Treatment Phase		Follow-up Phase
		Within 28 days before randomization	Day 1 of each cycle (± 48 hours) unless otherwise indicated (each cycle = 28 days)	EOT	Every 3 months (±7 days)
NOTE: **The EOT Visit** should occur within 30 days (±7 days) of last dose for subjects. **The Follow-up Phase** will continue until death, loss to follow-up, consent withdrawal for study participation, or study end, whichever occurs first.					
Screening/Administrative					
Informed consent	ICF must be signed before any study-related procedures	X			
Demography/ medical history		X			
Eligibility criteria	Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4, Source Documentation. Sponsor review of key eligibility and approval is required prior to randomization. Check clinical status again before first dose of study medication.	X			
Study Drug Administration (for details see also Section 6)					
Randomization	Within 3 days prior to the first dose	X			
Decitabine			Days 1, 2, 3, 4, and 5		
Talacotuzumab	Subjects randomized to Arm 1		Days 8 and 22 (± 24 hours)		
Safety Assessments					
Physical examination	Must be assessed within 3 days of Day 1 of each specified cycle, reviewed prior to starting the cycle and changes that are clinically significant must be reported on the AE page	X	X	X	
ECOG performance status evaluation	Must be assessed within 3 days of Day 1 of each specified cycle	X	X	X	
Vital signs	Temperature, blood pressure (BP) and heart rate (HR) will be assessed prior to each study treatment dosing • On talacotuzumab dosing days BP/HR are measured pre-dose and every 15 min during the first 90 min, and then at 30-min intervals for the remainder of the infusion. For the first infusion, obtain every 30 min post-infusion up to 1.5 hr after the infusion	X	X	X	

Procedure (Part B)	Notes	Screening Phase	Open-Label Treatment Phase		Follow-up Phase
		Within 28 days before randomization	Day 1 of each cycle (± 48 hours) unless otherwise indicated (each cycle = 28 days)	EOT	Every 3 months (±7 days)
Weight	Must be assessed within 3 days prior to dosing on Day 1 of each specified cycle, in case of weight loss of >10% within a cycle, the dose of study drug must be recalculated	X	X	X	
Height		X			
LVEF	MUGA scan is preferred. Echocardiogram can be used if MUGA is not available.	X	as clinically indicated	X	
ECG	QTcF will be assessed at the time of screening. If QTcF is >470 msec, repeat ECG 2 additional times approximately 3 – 5 minutes apart. Average the QTcF of all 3 ECGs to determine if the subject meets the QTc eligibility criteria	X	For subjects in Arm 1, ECG monitoring will occur on Cycle 1 Day 8 and Day 22 after the talacotuzumab IV infusion, then every other cycle thereafter on Day 22 after the talacotuzumab IV infusion. For subjects in Arm 2, ECG monitoring will occur on Cycle 1 Day 5 after the decitabine IV infusion and then every 2 cycles thereafter on Day 5 after the decitabine IV infusion.	X	
Concomitant medications	See Section 8 for detailed instructions; Includes transfusion requirements	Continuous from the time of signing of ICF until 30 days after last study drug dose			Concomitant medications for related AEs of Grade ≥3 and SAEs regardless of relationship; subsequent anticancer therapy

Procedure (Part B)	Notes	Screening Phase	Open-Label Treatment Phase		Follow-up Phase
		Within 28 days before randomization	Day 1 of each cycle (± 48 hours) unless otherwise indicated (each cycle = 28 days)	EOT	Every 3 months (±7 days)
Adverse events	See Section 12 for detailed instructions.	Continuous from the time of signing of ICF until 30 days after last dose of last study drug			Related AEs of Grade ≥3 and related SAEs; follow until resolution
Medical resource utilization	Information on all health care needs during treatment (eg, physiotherapist) to be collected	Continuous from the time of signing of the ICF until 30 days after the last dose of study drug			
Patient-reported outcomes					
FACT-Leu	PROs should be performed on Day 1 of each cycle before dosing and before any study tests or procedures are conducted.		X	X	Only at first FU
EQ-5D-5L			X	X	Only at first FU
Laboratory Assessments					
Hematology	At least the following parameters (hemoglobin, platelet count, absolute WBC count, absolute monocyte count, absolute basophil count, absolute eosinophil count absolute neutrophil count, absolute lymphocyte count, and peripheral blast count) must be assessed within 3 days of the indicated days of each cycle and results reviewed prior to starting dosing if applicable.	X	Days 1, 8, and 22	X	
Coagulation panel	aPTT, INR or prothrombin time (PT) must be assessed at screening and as clinically indicated afterward	X			
Clinical chemistry	At least the following parameters (AST, ALT, sodium, potassium, magnesium, BUN, phosphate, uric acid, calcium, alkaline phosphatase, creatinine, total bilirubin) must be assessed within 3 days of Day 1 of each cycle and results reviewed prior to starting the cycle.	X	X	X	
Assessment for active hepatitis or history of HIV		X			
Serum β-hCG or urine pregnancy test	For women of childbearing potential only	X	Only if clinically indicated		

Procedure (Part B)	Notes	Screening Phase	Open-Label Treatment Phase		Follow-up Phase
		Within 28 days before randomization	Day 1 of each cycle (± 48 hours) unless otherwise indicated (each cycle = 28 days)	EOT	Every 3 months (±7 days)
Disease Evaluations: A +/- 7-day window exists for completion of disease evaluation visits. Refer to Section 9.2 for details on efficacy evaluations					
Bone marrow aspirate/biopsy	A portion of each sample should be sent to the central lab for confirmation of disease status. A portion of the aspirate should be sent to the central lab for MRD and biomarker analysis at Screening, at suspected CR/CRi, then every disease assessment until relapse or EOT. Blood samples at matching time points will be taken for biomarker evaluations (CD123 expression, genomic characterization, and immunophenotyping). Molecular genetics and cytogenetics samples analyzed per the local standard of care at screening, at suspected CR/CRi and then every disease assessment until relapse or EOT	X (A biopsy can be used for confirmation of disease if taken within 6 weeks of randomization, but a fresh aspirate is required for MRD and biomarker analysis.)	• Every 2 Cycles starting at Cycle 2 (between Day 14 and 28) until treatment failure or relapse from CR/CRi or CCO • At time of suspected CR /CRi • At time of suspected treatment failure or relapse from CR/CRi	X (unless done within 2 weeks)	
Imaging	Per local standard of care and as clinically indicated. Report the disease assessment for AML related abnormalities including all sites of extramedullary disease	X	To repeat as clinically indicated per local standards. If extramedullary disease at baseline, repeat imaging (using the same modality) at time of best response		
Disease evaluation	Disease evaluation should be done based on information available; hematology, clinical presentation and bone marrow assessments.		• Every 2 Cycles starting at Cycle 2 (between Day 14 and 28) until treatment failure or relapse from CR/CRi or CCO • At time of suspected CR /CRi • At time of suspected treatment failure or relapse from CR/CRi	X	
Survival, subsequent therapy, other malignancies					X

Procedure (Part B)	Notes	Screening Phase	Open-Label Treatment Phase		Follow-up Phase
		Within 28 days before randomization	Day 1 of each cycle (± 48 hours) unless otherwise indicated (each cycle = 28 days)	EOT	Every 3 months (±7 days)
Pharmacokinetic, Pharmacodynamic, and Biomarker Assessments see TIME AND EVENTS SCHEDULE (PK AND BIOMARKERS) – TABLE 2B					

Abbreviations: AE=adverse event; ALT= alanine aminotransferase; AML=acute myeloid leukemia; ANC= absolute neutrophil count; AST= aspartate aminotransferase; β-hCG=beta human chorionic gonadotropin; CCO=clinical cut-off; CR= complete response; CRi= complete response with incomplete blood count recovery; BP=blood pressure; BUN= blood urea nitrogen; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; EQ=EuroQol; HBV: hepatitis B virus; HR=heart rate; ICF=informed consent form; INR= international normalized ratio; LDH= lactate dehydrogenase; LVEF= left ventricular ejection fraction; MRD= minimal residual disease; MUGA= multi gated acquisition scan; NK= natural killer (cells); PD=pharmacodynamics(s); PK=pharmacokinetic(s); PT= prothrombin time; aPTT= partial thromboplastin time; SAE=serious adverse event; T&E=Time & Events; WBC= white blood cell.

TIME AND EVENTS SCHEDULE – TABLE 1C [PART B] DURING AMENDMENT 6

Procedure (Part B)	Notes	Screening Phase	Open-Label Treatment Phase		Follow-up Phase
		Within 28 days before randomization	Day 1 of each cycle (± 48 hours) unless otherwise indicated (each cycle = 28 days)	EOT	Every 2 months (±7 days)
NOTE Following Amendment 6, which incorporated the IDMC's recommendations to close enrollment to the study and discontinue talacotuzumab treatment for subjects receiving talacotuzumab + decitabine and offer to continue decitabine alone, all subjects will continue to be followed for survival and subsequent anti-cancer therapy. During the treatment phase with decitabine, subjects will be monitored for serious adverse events.					
Serious adverse events	Follow until resolution		**X**		
Survival, subsequent therapy			**X**	**X**	**X**
EOT= end-of-Treatment; IDMC= Independent Data Monitoring Committee					

TIME AND EVENTS SCHEDULE – TABLE 1D [PART B] FOLLOWING AMENDMENT 7

Procedure (Part B)	
NOTE Following Amendment 7 and when 270 deaths have occurred or 6 months after the last subject is enrolled (whichever occurs first), follow up of subjects and data collection will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository.	

TIME AND EVENTS SCHEDULE (PK AND BIOMARKERS) – TABLE 2A [PART A]

PART A	Cycle 1						Cycle 2	Cycles 3 and 5	EOT[1]
	Talacotuzumab alone						Decitabine + Talacotuzumab		
	Day 1		Day 2	Day 3	Day 4	Day 8	Day 1	Day 8	
	predose	30 min after end of infusion	24 hour postdose	48 hour postdose	72 hour postdose	168 hours postdose	predose	Talacotuzumab predose	
Talacotuzumab PK sample[2]	X	X[3]	X	X	X	X	X	X	X
Immunogenicity Evaluation[2, 4]	X							X	X
PD/RO/biomarker sample (blood)[5]	X		X		X	X	X	X	X

Notes: EOT= End-of-Treatment (up to 30 days (+/- 7 days) after last dose of any study drug) Visit; PD= pharmacodynamics;
PK= pharmacokinetics; RO= receptor (CD123) occupancy

[1] The End-of-Treatment visit is after combination treatment.
[2] For subjects who experience a talacotuzumab infusion reaction, if possible, an unscheduled PK/immunogenicity sample should be drawn as soon as possible after the reaction.
[3] In the case that the talacotuzumab infusion is terminated before all the drug is administered, an additional PK sample will be taken immediately after the infusion is stopped.
[4] An aliquot from the talacotuzumab PK sample will be used to assess immunogenicity.
[5] Including assessment of NK cell activity by flow cytometry

TIME AND EVENTS SCHEDULE (PK AND BIOMARKERS) – TABLE 2B [PART B] UP TO AND INCLUDING AMENDMENT 5

PART B	Screening	Cycles 1 and 4								Cycle 2			EOT	First Follow Up
		Day 1	Day 5			Day 8		Day 9	Day 22	Day 23	Day 1	Day 8	Day 9		
		decitabine				talacotuzumab									
		Predose	Predose	5 minutes prior to end of infusion	1 hour after end of infusion	Predose	30 min after end of infusion	24 hour postdose	Predose (14d post 1st dose)	24hr post 2nd dose	Predose decitabine	Predose talacotuzumab			
Decitabine PK		X[1]		X[1]	X[1]										
Talacotuzumab PK sample[2,3]		X[4]				X	X[5]	X[1]	X	X[1]	X[1]	X		X	X
Immunogenicity Evaluation[2,3,6]						X						X		X	X
PD/RO sample (blood)		X				X		X[1,2]	X[2]	X[1,2]	X[1,2]	X[2]		X	
Biomarker sample for Methylation/ GEP (blood)		X	X			X			X					X	
Cytokine sample (blood): Cycles 1 and 2 only[7]						X	Cycle 1 only: at end of infusion and 2 hrs after (30 min collection is not taken)	X Cycle 1 only (if feasible)				X and at end of infusion and 2 hrs after	X (if feasible)		

Notes: EOT= End of Treatment; GEP= gene expression profiling; PD= pharmacodynamics; PK= pharmacokinetics; RO= receptor occupancy

[1] Sampling to be done for the first 120 subjects only
[2] Decitabine + talacotuzumab arm only.
[3] For subjects who experience a talacotuzumab infusion-related reaction, if possible, an unscheduled PK/immunogenicity sample should be drawn as soon as possible after the reaction.
[4] Cycle 4 only
[5] In the case that the talacotuzumab infusion is terminated before all the drug is administered, an additional PK sample will be taken immediately after the infusion is stopped.
[6] An aliquot from the talacotuzumab PK sample will be used to assess immunogenicity.
[7] For subjects who experience a talacotuzumab infusion-related reaction in any cycle, a blood sample should be drawn as soon as possible after the reaction and another approximately 1 day later, if feasible.

ABBREVIATIONS

ADCC	antibody-dependent cell cytotoxicity
AE	adverse event
ALT	alanine transaminase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC	area under the concentration-time curve
β-HCG	beta human chorionic gonadotropin
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence intervals
CL	total systemic clearance of drug after IV administration
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CR	complete response/remission
CRi	complete response with incomplete recovery
CRp	Complete response with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EFS	event-free survival
EOT	end-of-treatment
EQ	EuroQol
EU	European Union
FFPE	formalin-fixed paraffin-embedded
FLT3-ITD	FLT3-Internal Tandem Duplication
F/U	follow-up
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HBV	hepatitis B virus
HR	heart rate
HSC	hematopoietic stem cells
HSCT	hematopoietic stem cell transplantation
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IL-3	interleukin-3
INR	International normalized ratio
IRB	Institutional Review Board
IWRS	interactive web response system
LDH	lactate dehydrogenase
LSC	leukemic stem cells
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MFI	mean fluorescent intensity
MRD	minimal residual disease
MRU	medical resource utilization
MUGA	multi-gated acquisition scan

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	natural killer (cells)
NPM	Nucleophosmin
ORR	overall response rate
OS	overall survival
PD	Pharmacodynamics
pDC	plasmacytoid dendritic cell
PK	Pharmacokinetics
PQC	Product Quality Complaint
PRO	patient-reported outcomes
PT	prothrombin time
Q2W	every 2 weeks
RFS	relapse-free survival
RO	receptor occupancy
RP2D	recommended Phase2 dose
RT-PCR	reverse transcriptase – polymerase chain reaction
SAE	serious adverse event
SET	Study Evaluation Team
SNP	single nucleotide polymorphism
T&E	Time and Events (Tables)
WBC	white blood cells
WHO	World Health Organization
βc	beta common

1. INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by uncontrolled clonal expansion of hematopoietic progenitor cells.[26] As the second most common form of 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.[26,28] Advanced age associated with comorbidities, concomitant end-organ dysfunction, and poor performance status severely limits tolerance to cytotoxic chemotherapy. In addition, the biology of AML in the elderly also 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.[25] Although these patients may respond to chemotherapy, increased drug-related deaths offset clinical benefit.[20] As a consequence, major therapeutic advances associated with intensification of chemotherapies and the broader availability of curative allogeneic stem cell transplantation have primarily benefited the smaller subpopulation of younger AML patients. In contrast, the choice of more effective treatment options for the majority of elderly patients has remained very limited. In recent years, the hypomethylating agent decitabine (formulated product, DACOGEN®) has emerged as one of the preferred therapies for AML patients who cannot tolerate intense induction and consolidation chemotherapy.[5,25] Decitabine promotes cellular differentiation by reversing epigenetic suppression of gene expression, thus inducing durable responses in a subset of patients with AML. In a Phase 3 study, DACOGEN demonstrated a higher rate of complete responses (CRs) compared to the standard of care therapy of low-dose cytarabine (17.8% versus 7.8%).[21] Given the well described and predictable safety profile, multiple clinical studies are currently underway to improve the efficacy of decitabine in AML patients in novel combination regimens.

In this Phase 2/3 study, the safety and clinical efficacy of a combination of decitabine with the novel, therapeutic antibody talacotuzumab, directed against the α-subunit of the interleukine-3 receptor (CD123) overexpressed on leukemic blasts and leukemic stem cells (LSCs), will be explored in patients with previously untreated AML who are not eligible for intense induction chemotherapy.

For the most comprehensive nonclinical and clinical information regarding talacotuzumab and decitabine, refer to the latest version of the Investigator's Brochure and Addenda.[15,16] 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.

1.1. Talacotuzumab (JNJ-56022473; CSL362): Second Generation Anti-CD123 Antibody

Acute myeloid leukemia is a disorder of early hematopoietic progenitor cells, characterized by the proliferation and accumulation of immature, clonal, myeloid cells. Constitutive overexpression of the α-subunit of the interleukin-3 receptor ie, IL-3Rα, is a hallmark of the early AML progenitor cell population (ie, leukemic stem cells) as well as leukemic blasts. CD123 is unique to the IL-3 receptor and is responsible for the high specificity and low affinity binding of IL-3. Upon ligand binding, the α-subunit CD123 associates with the β_c-subunit (CD131) to form a high-affinity receptor complex initiating an intracellular signaling cascade through phosphorylation and activation of at least 3 distinct signal transduction pathways: the JAK/STAT-kinase, MAP-kinase-, and PI3-kinase-pathways. Under physiological conditions, activation of the IL-3 receptor induces proliferative, anti-apoptotic, and differentiating signals.[12]

Talacotuzumab (JNJ-56022473; CSL362) is a second generation antibody developed from the murine 7G3 anti-CD123 monoclonal antibody (mAb) in a stepwise process of humanization, affinity maturation, and Fc engineering. To enhance the cytotoxicity of the first-generation antibody CSL360, the proprietary Xencor (Xmab®) technology was applied and two amino acid mutations (S239D and I332E) were introduced into the Fc region.[16] These amino acid substitutions led to improved binding to CD16 (FcγRIIIa) on natural killer (NK) cells and significantly enhanced the ability to induce antibody-dependent cell-mediated cytotoxicity (ADCC).[3]

The talacotuzumab drug product that will be used in this study is produced in a different cell line with a different process compared with CSL362, the drug product used in the Phase 1 study CSLCT-AML-11-73 described below. Comparability testing of talacotuzumab and CSL362 has shown the antibodies to behave similarly in biophysical, biochemical, and preclinical assessments. The primary structure, charge heterogeneity, size heterogeneity, purity, higher order structure, and process impurities were found to be highly similar between CSL-362 and talacotuzumab. Pharmacodynamic (PD) studies in cynomolgus monkeys showed similar levels of biological activity between CSL362 and talacotuzumab (ie, basophil and pDC depletion; NK cell number and activity). Additionally, the PK profiles of talacotuzumab following 30 and 100 mg/kg IV dosing of cynomolgus monkeys are highly similar to those of CSL362. Following the first weekly IV dose, mean C_{max} and $AUC_{0\text{-}167h}$ of talacotuzumab are 91% and 94% of those observed for CSL362, respectively.

1.2. CSL362 Phase 1 Experience

CSL362 entered clinical development in 2012 in the ongoing study (CSLCT-AML-11-73; NCT01632852) entitled "A Phase 1 Study of CSL362 (Anti-IL3Rα/Anti-CD123 Monoclonal Antibody) in Patients with CD123+ Acute Myeloid Leukemia in Complete Remission or Complete Remission with Incomplete Platelet Recovery at High Risk for Early Relapse."

Design, Objectives: The study follows a 3+3 dose escalation design. The primary and secondary objectives are to evaluate the safety, pharmacokinetics, and immunogenicity of repeated doses of CSL362 in AML patients in CR. Exploratory endpoints include CSL362 effects on 1) CD123-expressing normal blood cells (basophils and plasmacytoid dendritic cells [pDCs], NK cells), 2) levels of serum cytokines, 3) binding to CD123 on monocytes, as well as 4) changes in the status of minimal residual disease (MRD) measured by flow cytometry and RT-PCR.

Study Therapy: The study therapy consists of IV CSL362 antibody infusion given every 14 days for 6 doses over a total treatment period of 12 weeks. The final evaluation for safety is conducted at Study Week 16. As of a data cutoff of 28 January 2015, 27 subjects had been enrolled and dosed.

Safety: The most frequent adverse event was severe infusion-related reaction characterized by fever and chills, nausea, vomiting, pain, headache, dizziness, breathlessness, chest pain, low or high blood pressure, rash, itchiness or weakness. The majority of these infusion-related reactions were observed in the first 2 dose cohorts (0.3 mg/kg and 1 mg/kg) in which premedication with hydrocortisone was not used. After mandatory pre-medication (including corticosteroids, see Section 6.3.2) was instituted and the infusion time was extended, no additional adverse events of severe infusion-related reaction were observed from the third cohort (0.75 mg/kg) onward up to the highest dose (9 mg/kg) given to date. A cohort exploring the safety of 12 mg/kg of CSL362 is underway.

For the 27 subjects treated with CSL362 as of the data cutoff of 28 January 2015, the most frequently reported (≥2 subjects) adverse events are summarized in Table 1.

Table 1: Treatment-Emergent Adverse Events Occurring in 2 or More Subjects in Study CSLCT-AML-11-73

	Number of Subjects (%)					
	CSL-362 0.3 mg/kg (N=6) n (%)	CSL-362 0.75 mg/kg (N=3) n (%)	CSL-362 1.0 mg/kg (N=6) n (%)	CSL-362 3.0 mg/kg (N=3) n (%)	CSL-362 9.0 mg/kg (N=9) n (%)	CSL-362 Overall (N=27) n (%)
Infusion-related reaction	6 (100)	2 (66.7)	3 (50.0)	0	5 (55.6)	16 (59.3)
Headache	4 (66.7)	1 (33.3)	3 (50.0)	1 (33.3)	2 (22.2)	11 (40.7)
AML Recurrent	1 (16.7)	2 (66.7)	1 (16.7)	0	4 (44.4)	8 (29.6)
Fatigue	1 (16.7)	2 (66.7)	2 (33.3)	0	2 (22.2)	7 (25.9)
Nausea	2 (33.3)	1 (33.3)	3 (50.0)	0	0	6 (22.2)
Chills	0	0	2 (33.3)	1 (33.3)	2 (22.2)	5 (18.5)
Dizziness	1 (16.7)	1 (33.3)	0	0	3 (33.3)	5 (18.5)
Pyrexia	0	0	1 (16.7)	0	3 (33.3)	4 (14.8)
Arthralgia	1 (16.7)	0	2 (33.3)	0	1 (11.1)	4 (14.8)
Hypotension	1 (16.7)	0	1 (16.7)	2 (66.7)	0	4 (14.8)
Vomiting	2 (33.3)	1 (33.3)	1 (16.7)	0	0	4 (14.8)
Diarrhea	0	0	2 (33.3)	0	2 (22.2)	4 (14.8)
Hypertension	2 (33.3)	0	1 (16.7)	0	0	3 (11.1)
Tachycardia	2 (33.3)	0	1 (16.7)	0	0	3 (11.1)
Constipation	0	1 (33.3)	1 (16.7)	0	1 (11.1)	3 (11.1)
Contusion	1 (16.7)	0	0	0	2 (22.2)	3 (11.1)
CRP Increased	0	0	1 (16.7)	1 (33.3)	1 (11.1)	3 (11.1)
Neuropathy peripheral	0	0	0	0	2 (22.2)	2 (7.4)
Chest discomfort	0	1 (33.3)	1 (16.7)	0	0	2 (7.4)
Chest pain	0	0	2 (33.3)	0	0	2 (7.4)
Oedema peripheral	0	1 (33.3)	0	0	1 (11.1)	2 (7.4)
Blood urea increased	0	0	1 (16.7)	1 (33.3)	0	2 (7.4)
Neutrophil count decreased	0	1 (33.3)	0	0	1(11.1)	2 (7.4)
Hyperglycaemia	1 (16.7)	0	0	1 (33.3)	0	2 (7.4)
Hypokalaemia	0	0	1(16.7)	1 (3.3)	0	2 (7.4)
Hypomagnesaemia	0	0	2 (33.3)	0	0	2 (7.4)
Nasopharyngitis	0	0	0	1 (33.3)	1 (11.1)	2 (7.4)
Upper respiratory tract infection	0	1 (33.3)	0	0	1 (11.1)	2 (7.4)
Urinary tract infection	0	0	1 (16.7)	0	1 (11.1)	2 (7.4)
Pain in extremity	0	1 (33.3)	0	0	1 (11.1)	2 (7.4)
Cough	0	0	0	1 (33.3)	1 (11.1)	2 (7.4)
Hypoxia	0	0	2 (33.3)	0	0	2 (7.4)
Thrombocytopenia	0	0	0	0	2 (22.2)	2 (7.4)

Data cutoff date: 28 January 2015
Source: CSLCT-AML-11-73 Interim report

The majority of adverse events were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2. Four subjects were reported with Grade 3 adverse events related to treatment with CSL362. One subject from the 0.3 mg/kg cohort was reported with Grade 3 hypertension. The remaining subjects with drug-related adverse events were from the 1.0 mg/kg cohort. One subject was reported with Grade 3 pyrexia, another subject was reported with Grade

3 infusion-related reaction, and another subject was reported with Grade 3 chills, chest pain, hypoxia, and infusion-related reaction. All subjects recovered from the adverse events. No Grade 4 drug-related events have been observed. Serious adverse events considered related to CSL362 treatment were reported for 3 subjects including 2 cases of infusion-related reaction and a single case of transient Grade 2 delirium associated with multiple concomitant medications. The safety data are preliminary and are subject to change.

Pharmacokinetics and Immunogenicity: The serum CSL362 concentrations appear to be dose proportional for doses ranging from 3 to 9 mg/kg. The terminal half-life determined after the 6th dose at 3 mg/kg was 4.7 days and the accumulation index after every 2 weeks dosing was 1.7 for maximum observed concentration (C_{max}) and 1.9 for the area under the curve (AUC). Low level anti-CSL362 antibody titers were detected coincident with trough concentrations of CSL362 in 6 of 18 subjects tested thus far, with no apparent effects on pharmacokinetics or association with adverse events.

Pharmacodynamics and Biomarkers: Indicative of the specific mode-of-action, ADCC, a rapid and complete in vivo depletion of CD123-expressing basophils and pDCs in the peripheral blood was observed for up to 15 days at CSL362 doses ≥3 mg/kg. Binding of CSL362 to CD123 on monocytes demonstrates rapid and sustained saturation over the 14-day inter-dosing interval at CSL362 dose levels ≥3 mg/kg.

1.2.1. Recommended Phase 2 Dose (RP2D):

Based on PK, PD, and safety data generated in the ongoing Phase 1 study, 9 mg/kg of CSL362 every 14 days has been selected as the dose and regimen for Phase 2 based on the following considerations:

Adequate PK and consistent saturation of CD123 target receptors on surrogate monocytes, and desired concentration of CSL362 at all sites of action, including bone marrow.

Based on preliminary data from the Phase 1 study, PK/PD modeling revealed that the concentration of 3 µg/mL of serum CSL362 is the upper boundary of the 90% CI of systemic concentration corresponding to at least 90% target engagement on monocytes.

While CD123 receptor occupancy on monocytes provides a convenient measure to monitor and characterize the PK/PD relationship in the peripheral compartment, it is important to note that a key pharmacological target of CSL362 is in the leukemic stem cell niche in the bone marrow. Only a fraction of an antibody dose (approximately 30%) is distributed to the bone marrow,[1] and it is anticipated that the PD effect may be reduced in the bone marrow at doses that completely saturate peripheral targets. In addition, patients with active AML may also have higher leukemic blasts and higher levels of CD123 targets than the patient population in the Phase 1 study CSLCT-AML-11-73. Thus, higher systemic exposure may be required in order to ensure sustained target saturation throughout the dosing interval at the site of action.

Taking into consideration the serum CSL362 concentration of 3 µg/mL (which ensures peripheral target engagement and the limited biodistribution into the site of action), the desired

target serum concentration of CSL362 is projected to be 9 µg/ml, approximately 3 fold higher to ensure adequate and sustained exposure at the site of action.

Based on simulations from a preliminary population PK model, 9 mg/kg every 14 days is the selected dose/dosing regimen to achieve sustained exposure above 9 µg/mL throughout the dosing interval.

Acceptable safety profile

No DLT or AEs ≥Grade 3 related to CSL362 occurred in subjects dosed at 9 mg/kg every 14 days. Premedication with hydrocortisone and a prolongation of the infusion time to 3 hours effectively protected against Grade ≥ 3 infusion reactions. Since implementation of the protocol amendment to premedicate with hydrocortisone, no subjects treated at the 3 mg/kg or 9 mg/kg dose levels experienced a severe (Grade ≥ 3) infusion-related reaction. A cohort testing a higher dose of 12 mg/kg every 14 days is currently open for enrollment in the Phase I trial (CSLCT-AML-11-73). In summary, 9 mg/kg every 14 days is a well-tolerated dose and is the lowest dose that provides adequate exposure and sustained target saturation at the site of action throughout the entire dosing interval.

1.3. DACOGEN (decitabine)

Decitabine (5 aza-2'-deoxycytidine) has a unique molecular mode-of-action. As a deoxycytidine nucleoside analog decitabine is primarily an inhibitor of DNA methyltransferase interfering with cytosine methylation in DNA.[15] At low doses decitabine induces a hypomethylating effect when incorporated into DNA thus, reversing the aberrant epigenetic silencing of critical tumor suppressor genes through DNA hypermethylation. However, at higher doses decitabine may produce direct cytotoxic effects via DNA strand breaks.[8] These activities of decitabine have been shown to correlate with the re-expression of silenced genes, cellular differentiation as well as with the inhibition of cell growth and the induction of apoptosis.[24]

In a randomized Phase 2 study comparing three dosing regimens, DACOGEN at a dose of 20 mg/m^2 per day infused IV over one hour on 5 consecutive days every 28 days optimally induced hypomethylation and provided the best clinical efficacy.[19] With this regimen the half-life of decitabine was determined to be approximately 30 minutes and systemic accumulation was not observed. In a randomized Phase 3 study conducted in patients with newly diagnosed AML and poor- or intermediate-risk cytogenetics, DACOGEN given as the 5-Day regimen demonstrated superior clinical efficacy compared to a treatment choice of supportive care or low-dose cytosine arabinoside.[21] Decitabine treatment resulted in significantly improved rates of CR and CR without platelet recovery (CRp) compared with treatment choice.[26] While the primary analysis for OS demonstrated an advantage favoring decitabine (7.7 months versus 5 months), which was however not statistically significant (p=0.108), an unplanned analysis of more mature survival data reached statistical significance (p=0.037).[26] Based on the results of this Phase 3 study, DACOGEN was approved in the European Union (EU) and 21 other countries (as of November 2014) for the treatment of adult patients age ≥ 65 years with newly diagnosed de novo or secondary acute myeloid leukemia (AML), who are not candidates for standard induction chemotherapy. In addition, in the USA decitabine is a recommended

treatment option for AML patients 60 years or older who are not candidates for intensive chemotherapy according to the guidelines of the National Comprehensive Cancer Network.[28]

The adverse event profile of decitabine primarily includes myelosuppression (neutropenia, anemia, and thrombocytopenia) and consequences of myelosuppression (infections, fatigue, and febrile neutropenia). Nonhematologic adverse events associated with decitabine include nausea, vomiting, diarrhea, stomatitis, and alopecia. Generally these toxicities can be managed with supportive care measures, pharmacologic intervention, and dose adjustments. Specific information on the safety of decitabine is outlined in the prescribing information and can be found in the Investigator Brochure.[15]

1.4. Overall Rationale for the Study

Similar to normal hematopoiesis, AML arises from a distinct population of leukemic stem cells (ie, LSCs) residing in the bone marrow that are able to self-renew and to propagate into leukemic blasts.[37] In contrast to the highly proliferative blast cells, the pool of LSCs is often not affected by cytotoxic chemotherapies because these stem cells (i) persist in a quiescent G0 cell cycle phase and are not actively dividing (ii) reside in the bone marrow microenvironment that provides protection against apoptosis, and (iii) overexpress the multidrug resistance protein that enhances drug efflux.[30]

Effective AML therapies have to target both the highly proliferative and chemotherapy-sensitive leukemic blast cells as well as the quiescent and resistant LSC pool in order to achieve higher rates of durable CRs and more importantly longer disease-free- and overall survival (OS). As an antimetabolite and hypomethylating agent, decitabine targets proliferating leukemic blast cells and is a recognized treatment option for the therapy of patients with AML who are not eligible for intense chemotherapy or HSCT. Among different agents that may be used to deplete the LSC pool and kill leukemia blasts, antibodies that are able to penetrate the bone marrow and are capable of eliciting a potent, cytotoxic immune response have the potential to improve clinical outcomes.[11,29] Effective targeting of the LSC pool is dependent on the ability of the antibody to specifically ablate leukemic blasts and the population of LSCs without affecting the regeneration of normal hematopoietic stem cells.

Although the exact phenotypes of CD34+/CD38- AML stem cells remain controversial, the constitutive over-expression of the CD123 antigen is common.[11] CD123 over-expression on LSCs is conserved on the emerging leukemic blast cells and constitutes a marker of poor clinical prognosis because of the association with (i) known adverse immune-phenotypes such as FLT3 internal tandem duplication (FLT3-ITD), (ii) a lower rate of complete responses following conventional chemotherapy and (iii) shorter disease-free survival and overall survival (OS).[10,34,36] Levels of CD123 in normal hematopoietic stem cells and early hematopoietic progenitor cells are considerably lower than the overexpression found on LSCs and blasts in AML.[10,17] Results from the ongoing Phase 1 study of CSL362 suggest that targeting CD123-overexpressing LSC and leukemic blast cells with an anti-CD123 antibody may not affect normal hematopoiesis.

The safety assessments and confirmation of the RP2D in Part A of this study have been designed to supplement the biophysical and preclinical toxicology comparability testing of the anti-CD123 monoclonal antibody produced in different Chinese hamster ovary cell lines; CSL362 was produced in the CHO-S cell line and used for the Phase 1 study while talacotuzumab was produced in GS-CHOK1SV cells and will be used for all subsequent clinical studies. Results from preclinical testing are provided in Section 1.1 and the talacotuzumab (JNJ-56022473) Investigator's Brochure.[16]

The scientific rationale for the seamless Phase 2/3 portion of this study (Part B) is that the combination of decitabine and talacotuzumab may have a complimentary/synergistic effect on the leukemic cells.

The complimentary and as such more pronounced therapeutic efficacy of the combination regimen is expected to evolve from the different underlying mechanisms of action and the different leukemic cell populations targeted by the two agents. Therapy with decitabine reverses the hypermethylation-induced gene silencing and restores the proliferation control and the apoptosis sensitivity in proliferating leukemic blast cells. Talacotuzumab has the potential to elicit a direct immunotherapeutic effect against CD123 overexpressing quiescent LSCs and leukemic blasts through re-direction of NK-cells and induction of ADCC. These 2 agents are also expected to have non-overlapping toxicity profiles; decitabine is primarily myelosuppressive while the most frequent toxicity from administration of talacotuzumab is infusion reactions. Additionally, the administration of the 2 agents is sequential and staggered, minimizing the likelihood of toxicities due to the combination treatment.

In addition, the combination of decitabine and talacotuzumab may also lead to a potent, synergistic therapeutic effect. It has been shown that decitabine at continuous, low doses improves innate immunity by stimulating proliferation, survival, and activity of NK-cells.[23,31] In an initial series of experiments, decitabine treatment stimulated and augmented NK reactivity measured by IFNγ mRNA expression and protein release in response to activating stimuli in vitro.[31] In a follow-up study, it was demonstrated that exposure to decitabine at low doses (7 mg/m^2) over 5 days decreased the expression of inhibitory receptors (eg, KIR) and increased the expression of activating receptors (eg, NKG2D and NKp44) on activated NK cells in vitro.[23] The authors propose that novel therapeutic strategies involving decitabine should aim at combining the "direct effect of decitabine on malignant cells with its ability to enhance reactivity of NK cells in immunotherapeutic approaches".[31] Thus, decitabine exposure at the approved low dose of 20 mg/m^2 over the extended treatment period of 5 days may stimulate innate NK cell-mediated immunity and thus enhance the ADCC-dependent anti-leukemic activity of talacotuzumab.

In the dosing schedule proposed for the combination regimen, talacotuzumab will be given after decitabine in order to take advantage of the potential stimulation of the innate immunity. This will allow the combination of full therapeutic doses of decitabine (eg, 20 mg/m^2) and talacotuzumab (9 mg/kg, confirmed in Part A). Additionally, the safety profiles of the agents indicate that toxicities are not overlapping and adverse events will be managed with monitoring and supportive care.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objectives

Part A: to assess the safety of talacotuzumab monotherapy and confirm the RP2D in subjects with AML for whom experimental therapy is appropriate (as assessed by their treating physician).

Part B: The primary objectives of the study are to assess CR rate and OS in subjects with previously untreated AML who are not eligible for intense induction chemotherapy and who are randomly assigned to receive decitabine plus talacotuzumab at the RP2D or decitabine alone.

Secondary Objectives (Part B)

The secondary objectives are:

- To assess EFS;
- To determine the overall response rate (ORR) defined as rate of complete response (CR) and complete response with incomplete blood count recovery (CRi);
- To determine the rate of CR plus MRD negative CRi
- To assess the relapse-free survival (RFS);
- To assess time to response and duration of response for subjects who achieve CR/CRi;
- To assess minimal residual disease (MRD);
- To assess the safety profile of talacotuzumab in combination with decitabine;
- To assess the pharmacokinetics of talacotuzumab and decitabine alone and in combination;
- To assess the immunogenicity talacotuzumab alone (Part A) and in combination with decitabine (Part B);
- To assess patient-reported outcomes (PROs) using the FACT-Leu and EQ-5D-5L.

Exploratory Objectives

The exploratory objectives are:

- To explore PK/PD relationships of talacotuzumab through analysis of talacotuzumab PK, biomarkers, PD markers, and clinical end points;
- To explore biomarkers predictive of clinical response;
- 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).

2.1.2. Endpoints

Primary Endpoint (Part A)

Safety and DLT determination

2 Primary Endpoints (Part B)

- CR rate
- OS

Secondary Endpoints (Part B)

- EFS, defined as the time from randomization to treatment failure, relapse from CR/CRi, or death from any cause, whichever occurs first. Treatment failure is defined as >25% absolute increase in the bone marrow blast count from baseline to the present assessment.
- ORR rate (CR + CRi);
- Rate of CR plus MRD negative CRi;
- Time to response, defined for subjects who achieved best response of CR or CRi as time from randomization to achieving the best response;
- Duration of response, defined for subjects who achieved best response of CR or CRi as time from achieving CR or CRi to relapse;
- Relapse-free survival (RFS) defined for subjects who achieved CR or CRi as the time from achieving CR or CRi to disease relapse or death from any cause;
- Safety profile;
- Pharmacokinetics;
- Immunogenicity;
- MRD;
- Patient-reported outcomes (PROs) using the FACT-Leu and EQ 5D 5L.

Exploratory Endpoints (Part B))

- Pharmacokinetic/pharmacodynamic relationships associated with biomarkers, PD markers and clinical end points;
- To explore biomarkers associated with clinical response;
- Medical resource utilization.

2.2. Hypothesis

In patients with previously untreated AML who are not eligible for intense induction chemotherapy it is hypothesized that treatment with a combination regimen of decitabine and talacotuzumab as compared with decitabine alone, will improve CR rate or extend survival or both.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a 2-part, open-label, multicenter, seamless Phase 2/3 study conducted in subjects with AML who are suitable for experimental therapy (Part A) and in subjects with untreated AML who are not eligible for intense induction chemotherapy or hematopoietic stem cell transplantation (HSCT; hereafter referred to as not eligible for intense chemotherapy) (Part B).

In Study Part A, the safety, PK and PD profile, and RP2D of 9 mg/kg talacotuzumab will be confirmed. In Part B, subjects will be randomized 1:1 into either Arm 1 (decitabine + talacotuzumab) or Arm 2 (decitabine alone). Blood and bone marrow sampling for disease assessment, PK, PD, and biomarkers will be mandatory for all subjects in the study.

Part A: Recommended Phase 2 Dose Confirmation

The safety assessments and confirmation of the RP2D in Part A of this study have been designed to supplement the biophysical and preclinical toxicology comparability testing of the anti-CD123 monoclonal antibody produced in different Chinese hamster ovary cell lines. Comparability testing of talacotuzumab and CSL362 has shown the antibodies to behave similarly in biophysical, biochemical, and preclinical assessments. See Section 1.1 and the talacotuzumab (JNJ-56022473) Investigator's Brochure[16] for information regarding the biophysical and preclinical toxicology studies.

Six subjects will be enrolled in Part A and receive 1 dose of talacotuzumab at 9 mg/kg on Day 1 as a 180-minute IV infusion. Dose-limiting toxicities (DLTs) will be assessed during the DLT evaluation period (Cycle 1; 14 days). All subjects will receive premedication with hydrocortisone or equivalent IV steroid to prevent infusion reactions. Refer to the Dosage and Administration schedule (Section 6 Dosage and Administration) for further detail.

Pharmacokinetic and pharmacodynamic assessments will be conducted during the 14-day talacotuzumab evaluation period (see Time and Events Schedule Table 2A). Upon completion of dosing, there will be a review of all available study data by a Study Evaluation Team (SET) to

confirm the RP2D of 9 mg/kg talacotuzumab. If no DLTs are observed or are observed in 1 of the 6 subjects, the dose of 9 mg/kg talacotuzumab may be established as the RP2D by the SET. If DLTs are observed in ≥2 of the 6 subjects, Part A may continue with additional enrollment of 3 to 6 subjects at a lower dose level of talacotuzumab to be determined by the SET.

Dose-limiting toxicities (DLT) are adverse events that occur up to the end of Cycle 1, meet the following criteria, and are confirmed by the SET:

- CTCAE Grade 4 non hematological toxicities
- CTCAE Grade 3 non hematological toxicities that persists for ≥ 7 days despite best supportive care according to institutional standards.

After the RP2D for talacotuzumab is confirmed, Part B can be initiated.

Subjects in Part A will continue on study (remaining in Part A) and start subsequent cycles of the combined study therapy with decitabine at the dose of 20 mg/m^2 IV on Day 1 to Day 5 followed by 9 mg/kg (or a lower dose if determined by the SET) talacotuzumab on Day 8 and Day 22 of a 28-day cycle. Subjects will continue study therapy as outlined in Section 6 until treatment failure (as defined in Section 9.2.1.1), relapse from CR/CRi, unacceptable toxicity, or death as described in Section 10.2.

Part B:

Part B is designed to be a seamless Phase 2/3 study with 2 primary endpoints, CR rate and OS. Subjects will be randomized in a 1:1 ratio to receive either decitabine + talacotuzumab (Arm 1) or decitabine alone (Arm 2). Randomization will be stratified by baseline ECOG performance status (0-1 versus 2) and type of AML (de novo versus secondary). The study will have 3 interim analyses. The first interim analysis will occur after approximately 80 subjects (40 subjects per arm) have been randomized and followed for at least 4 months. Guided by predefined statistical criteria based on CR and CR+CRi rates and central review of data (see Section 11.2), the study will either continue enrollment to the full pre-specified Phase 3 sample size of 400 subjects or discontinues enrollment. A total of approximately 120 subjects are expected to have been randomized by the time the outcome of the interim analysis is available. No changes in design elements are planned based on this interim analysis.

If the enrollment continues to 400 subjects (approximately 200 subjects per arm), the pre-specified design elements are:

- A second interim analysis occurs after 160 subjects (approximately 80 subjects per arm) have been randomized and followed for at least 4 months; this is the final analysis for CR and the first interim analysis for OS. The study will not be stopped on the basis of the CR results;
- A third interim analysis (ie, the second interim analysis of OS) will be conducted when 180 deaths have occurred;
- The final analysis of OS will take place when 270 deaths have occurred or 6 months after the last subject was enrolled whichever occurs first.

If the study stops enrollment based on the pre-specified criteria, it is expected that approximately 120 subjects will have been randomized. These subjects will continue to be followed. The clinical cut-off in this case will be when 90 EFS events have occurred.

Part A and Part B: Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 28 days prior to start of study therapy in Part A or up to 28 days prior to randomization in Part B. The Treatment Phase begins with start of study therapy (Part A) or randomization (Part B) and continues until the End-of-Treatment Visit. The Follow-up Phase begins immediately following the End-of-Treatment Visit, and continues until death, loss to follow up, consent withdrawal for study participation, or study end, whichever occurs first. Subjects will receive study treatment until treatment failure, relapse from CR/CRi, or death, unless discontinued early because of unacceptable toxicity, or other reasons specified in Section 10.2. The median time to response in a Phase 3 study of DACOGEN was 4.3 months.[6] Additional responses were noted after 4 months. For this study, it is recommended that for subjects who do not have evidence of treatment failure to continue decitabine treatment. Subjects in Arm 1 may discontinue one of the study agents (decitabine or talacotuzumab) because of unacceptable toxicity and continue treatment with the other agent until treatment failure, relapse from CR/CRi, or death, unless discontinued early because of unacceptable toxicity.

All study evaluations will be conducted according to the Time and Events Schedule Tables 1A, 1B,1C and 1D. Disease evaluations will include clinical presentation, peripheral blood, and bone marrow assessments. Disease status will be evaluated according to the modified "Response Criteria in AML" (Section 9.2.1.1).[9] During the Treatment Phase, safety evaluations will include adverse event monitoring, vital sign measurements, physical examinations, clinical laboratory parameters (hematology and chemistry), and Eastern Cooperative Oncology Group (ECOG) performance status. Additional blood samples will be drawn for assessment of pharmacokinetic and pharmacodynamics parameters and a pharmacogenomics blood sample will be collected to allow for exploratory biomarker activities.

Study Evaluation Team (SET): A SET will monitor preliminary safety and study conduct data on an ongoing basis during the study for Part A. The SET will consist of selected investigators, sponsor medical monitors, the sponsor's statistician, and the sponsor's clinical pharmacologist, or their designees. The scope of this safety review will be detailed in the SET Charter. Decisions regarding DLT determination, dose de-escalation, changes in the timing of pharmacokinetic or pharmacodynamic sampling, exploration of alternative schedule(s), cycle duration, or other study conduct recommendations, will be made by the SET and documented in a SET decision document and distributed to investigators. The Institutional Review Board (IRB) will be notified before implementation of any SET decision, if required. This document will be provided in the sponsor's instruction manual and retained in the study master file and in the study center's files.

During Part A, the SET will review all available data upon completion of the 14-day period following talacotuzumab treatment (Cycle 1) to determine DLTs, and subsequently, will confirm the RP2D. Additionally, accumulated safety data will be reviewed for subjects in Part A who are receiving combination therapy prior to the start of Part B. The following data will be reviewed as available: study compliance (including drug exposure as applicable), adverse event and safety profile, PK, and PD. The SET recommendations will be documented in a SET recommendations document and distributed to investigators.

Independent Data Monitoring Committee: An Independent Data Monitoring Committee (IDMC) will be established to evaluate safety and efficacy data collected during Part B of the study.

The IDMC will conduct a safety review of accumulated data from Part A and Part B when approximately 20 subjects from Part B (10 subjects from each arm) have been enrolled and followed for at least 1 month to assess the safety and tolerability of the combination regimen.

The IDMC will also be responsible for reviewing the formal efficacy interim analyses as described in Section 11.2, and make recommendations for the study conduct. An IDMC charter will describe the policies and procedures.

Independent Central Review: In addition to evaluations by investigators, disease status will be reviewed and determined by an independent central review in a blinded fashion. A charter will describe the policies and procedures in detail.

Note: After review of the data from Interim Analysis #2, the IDMC informed the Sponsor that the futility criterion for OS was met and that the CR rate did not meet per-protocol defined statistical significance. Given the lack of efficacy advantage of talacotuzumab + decitabine versus decitabine alone, the incidence of infusion-related reactions, and the complexities with premedications for drug administration, the benefit/ risk ratio is not favorable to continue treatment with talacotuzumab. The IDMC recommended closure of enrollment to the study and that subjects receiving talacotuzumab + decitabine should discontinue talacotuzumab treatment and may continue decitabine alone, according to Principal Investigator decision and subject agreement. All subjects will continue to be followed for survival and subsequent anti-cancer therapy. During the treatment phase with decitabine, subjects will be monitored for serious adverse events.

The end of study data collection is defined as when 270 deaths have occurred or 6 months after the last subject is enrolled, whichever occurs first. At that time, follow up of subjects will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository as described under Amendment 7.

3.2. Study Design Rationale

Rationale for Single Agent Talacotuzumab Monotherapy in Part A

Studies with CSL362 identified 9 mg/kg as the RP2D. Talacotuzumab is produced in a different cell line with a different process compared with the Phase 1 study (CSLCT-AML-11-73) CSL362 drug product. To confirm the safety and RP2D of talacotuzumab, a safety run-in period of talacotuzumab at 9 mg/kg will be evaluated first as monotherapy in Part A of this study.

Rationale for DACOGEN

Decitabine is an appropriate comparator in this study as it is approved for the treatment of this AML population in the European Union (EU) and 21 other countries (as of November 2014) and is a treatment option recommended in treatment guidelines such as the National Comprehensive Cancer Network.[9,28]

The proposed schedule of decitabine administered at a dose of 20 mg/m^2 body surface area by IV infusion over 1 hour repeated daily for 5 consecutive days (ie, 5 doses per treatment cycle) is outlined in more detail in the prescribing information. The total daily dose of decitabine must not exceed 20 mg/m^2 and the total dose per treatment cycle must not exceed 100 mg/m^2.

Rationale for Dose of Talacotuzumab

Safety: The talacotuzumab dose and schedule for this study was planned using CSL362 results from a Phase 1 study (CSLCT-AML-11-73). CSL362 has been deemed safe and well tolerated as no AE $\geq$ CTCAE Grade 3 has occurred in 9 subjects dosed at 9 mg/kg every 14 days in the CSL-sponsored Phase 1 study. Despite the initially observed adverse event of severe (CTCAE Grade 3) infusion-related reaction at low doses, no subject at the 9-mg/kg dose level experienced a severe infusion related reaction after the institution of mandatory pre-medication and a prolonged infusion time to 3 hours.

Pharmacokinetics: With CSL362, the 9 mg/kg dose exhibits predictable PK above the nonlinear pharmacokinetic range where higher clearance and shorter half-life was observed at lower doses. Additionally, the half-life of 4 to 5 days supports the every 14-day dosing frequency. At 9 mg/kg, the trough concentration of CSL362 from the majority of subjects is expected to exceed the estimated concentration needed to saturate the CD123 target as measured by the peripheral marker monocytes. This dose is selected to ensure sustained target saturation throughout the dosing period, particularly considering that 1 of the therapeutic targets is anticipated to be the leukemic stem cell niche in the bone marrow.

Pharmacodynamics: For CSL362, the pharmacodynamic pattern and kinetics of biomarkers, including basophils, pDC cells, NK cells, monocytes, etc. are generally comparable regardless of the cycle number. Aside from CD123 expressing cell types, CSL362 at 9 mg/kg does not seem to significantly affect other cells, or only affect transiently with return to baseline expected within 3 days, as in the case of NK cells. In summary, 9 mg/kg every 2 weeks is a safe dose within the linear PK dose range that is expected to provide adequate exposure and sustained target saturation throughout the dosing interval for both peripheral and bone marrow blasts and LSCs.

Rationale for Talacotuzumab Dose in Combination with DACOGEN

Decitabine has a safety profile that allows for its use as an outpatient therapy for elderly and physically impaired patients with AML.[25] Treatment with decitabine is associated with myelosuppression and adverse events related to myelosuppression (ie, thrombocytopenia, anemia, neutropenia, and febrile neutropenia) which are however common in both treated and untreated patients with AML.[15] Decitabine administered at the recommended dose (20 mg/m^2) and schedule (Days 1 to 5) currently is being tested in combination with a variety of experimental compounds.[25,26] The safety and PK data obtained for CSL362 in the ongoing Phase 1 study support the proposed combination regimen with decitabine using full doses of both agents. The safety profiles of both agents are considerably different. While treatment with decitabine may exacerbate the myelosuppression frequently observed in patients with AML, no impact on normal hematopoiesis was observed in AML patients in CR exposed to increasing doses of CSL362. This Phase 1 safety observation supports the scientific hypothesis that CD123 is differentially expressed on normal hematopoietic stem cells and LSCs. Therefore, by specifically targeting the LSCs and the emerging leukemic blast cells, the addition of talacotuzumab may not lead to an aggravation of the myelosuppression or extension of the time of hematopoietic recovery observed in AML patients receiving decitabine. Lastly, pharmacokinetic drug-drug interaction between decitabine and talacotuzumab is not expected given the different absorption, distribution, metabolism, and excretion (ADME) properties and metabolic pathways utilized by these agents.

Rationale for Randomization

In Part B, subjects will be randomized to receive either decitabine + talacotuzumab (Arm 1) or decitabine alone (Arm 2). Randomization will minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Additionally, enrollment into the treatment arms is stratified by baseline ECOG performance status score (0-1 versus 2) and type of AML (de novo versus secondary), prognostic factors known to affect clinical outcomes.[9]

After Interim Analysis #2, enrollment to the study was closed. Subjects receiving talacotuzumab + decitabine (Arm 1) stopped talacotuzumab treatment and were allowed to continue to receive decitabine alone, according to Principal Investigator decision and subject agreement. This was based on an IDMC review that noted a lack of efficacy advantage of talacotuzumab + decitabine versus decitabine alone, the incidence of infusion-related reactions, and the complexities with premedications for drug administration that made the benefit/ risk ratio not favorable to continue treatment with talacotuzumab.

Rationale for Primary Endpoints

For this Phase 2/3 study, CR rate and OS are chosen as the 2 primary endpoints for the reason that a higher CR rate would be an early and clinically meaningful measure of efficacy and an improvement in OS would demonstrate the broadest and most meaningful measure of treatment benefit.[32]

Rationale for Biomarker Evaluation

Biomarker samples will be collected to evaluate the mechanism of action of the combination of decitabine + talacotuzumab, to establish the threshold of CD123 expression needed for clinical response, and to help explain inter-individual variability in clinical outcomes or to identify population subgroups that respond differently to decitabine + talacotuzumab or decitabine alone.

Rationale for Pharmacodynamic Marker Evaluation

Previous CSL362 pre-clinical and clinical studies in subjects with AML demonstrated that CD123-positive pDC and basophils are reliable cellular pharmacodynamic markers for CSL362 activity.[3,33] These cells were completely depleted within hours of CSL362 infusion and depletion was sustained for ≥ 15 days at doses ≥ 3.0 mg/kg. Natural killer cells are critical to the mechanism of action of talacotuzumab (CSL362) and quantification may reveal an association with clinical response. Natural killer cell counts are reduced in the first few hours after dosing but stabilized at Day 3 and thereafter, indicating that this fluctuation may be caused by NK cell redistribution.[33]

Rationale for Assessment of CD123 Expression

CD123 is expressed in AML blasts and LSCs in a large percentage of AML patients (75-89%).[14,17,27] The percentage of CD123+ leukemic blasts at diagnosis has been correlated with a poor response to intensive chemotherapy.[36] In a study by Ehninger,[10] 78% of newly diagnosed AML patients had AML blasts that were positive for CD123 expression. The cutoff for positive flow measurements in this study was set to >10, based on the geometric mean fluorescence intensities (MFIs) of CD123 in blasts in relation to the MFIs of lymphocytes (considered negative for CD123).[10]

Rationale for Minimal Residual Disease Assessment

Assessment of minimal residual disease (MRD) is becoming an important evaluation to determine the depth of response beyond clinical CR in AML and other hematologic malignancies,[13] and it has been shown that MRD assessment adds prognostic value beyond both karyotype and specific gene mutations.[2,18]

Rationale for Immunophenotyping

The activity of talacotuzumab depends on its ability to engage its target (CD123) and recruit effector cells of the immune system for cell killing. Therefore, the ultimate activity of this agent depends not only on expression of the target by AML blasts and LSCs, but also on the fitness of the host immune system. Therefore, we will determine the state of the host's immune system. In addition, the biomarker plan will attempt to address the effect of decitabine on the host immune system, with particular attention to NK effector cell number and function.

4. SUBJECT POPULATION

The screening period for eligible subjects for this study will be performed within 28 days before the first dose of study therapy (Part A) or within 28 days before randomization (Part B).

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of the number of subjects, refer to Section 11.3, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study. These criteria are applicable for both Part A and Part B of the study unless otherwise noted.

1 Criterion Modified per Amendment 1

1.1 Criterion Modified per Amendment 2
1.2 AML according to WHO 2008 criteria[35] fulfilling all of the following criteria:

For Part A:
Patients with AML (treatment naive or relapsed) for whom experimental therapy is appropriate (as assessed by their treating physician);

For Part B:

- ≥75 years of age or
- ≥65 up to 75 years of age and have at least one of the following:
  - Congestive heart failure or ejection fraction ≤50%
  - Creatinine >2 mg/dL, dialysis or prior renal transplant
  - Documented pulmonary disease with lung diffusing capacity for carbon monoxide (DLCO) ≤65% of expected, or forced expiratory volume in 1 second (FEV1) ≤65% of expected or dyspnea at rest requiring oxygen
  - ECOG performance status of 2
  - Prior or current malignancy that does not require concurrent treatment
  - Unresolved infection
  - 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
- De novo or secondary AML (post myelodysplastic syndrome [MDS] or myeloproliferative neoplasm [MPN] or after leukemogenic chemotherapy);
- Previously untreated AML (except: emergency leukopheresis and/or hydroxyurea during the screening phase to control hyperleukocytosis but must be discontinued at least one day prior to start of study therapy);
- Not eligible for an allogeneic hematopoietic stem cell transplantation.

2. ECOG Performance Status score of 0, 1 or 2.
3. Criterion Modified per Amendment 1

3.1 Criterion modified per Amendment 2
3.2 Criterion modified per Amendment 3
The following clinical laboratory values at screening:

Hematology:

- Platelet count ≥ 10 x 10^9/L (with or without transfusions)
- White blood cell count (WBC) ≤ 40 x 10^9/L (Note: leukopheresis or hydroxyurea is permitted to decrease WBC count but must be discontinued 1 day prior to start of study therapy)

Hepatic:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 2.5 times ULN; for subjects with leukemic infiltration of the liver, AST and ALT ≤ 5 times ULN is permitted

Total Bilirubin ≤ 1.5 times ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin

4. A woman must be either:
   - Not of childbearing potential: postmenopausal (>45 years of age with 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 subjects participating in clinical studies for at least 3 months: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject)

     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.
5. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at screening.
6. 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.
7. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study. These criteria are applicable for both Part A and Part B of the study unless otherwise noted.

1. Acute promyelocytic leukemia with t(15;17), or its molecular equivalent (PML-RARα).
2. **For Part B only:** Known leukemic involvement or clinical symptoms of leukemic involvement of the central nervous system.

3. Criterion Modified per Amendment 1

3.1 Subjects who received prior treatment with a hypomethylating agent.

4. **For Part A only**: Subjects who did not recover from all clinically significant toxicities (excluding alopecia and hematologic toxicities) of any previous surgery, radiotherapy, targeted therapy, or chemotherapy to less than or equal to Grade 1;
5. Criterion modified per Amendment 1

5.1 Criterion Modified per Amendment 2
5.2 A diagnosis of other malignancy that requires concurrent treatment.
6 Criterion Modified per Amendment 2
6.1. Any uncontrolled active systemic infection that requires treatment with IV antibiotics

7. Criterion Modified per Amendment 1

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

8. Criterion Modified per Amendment 2
8.1
Active systemic hepatitis infection requiring treatment or other clinically active liver disease
9. Criterion Modified per Amendment 2
9.1 Criterion modified per Amendment 3
Unstable angina
10. Criterion Removed per Amendment 2
10.1
11. QTcF > 470 ms, or QTcF prolongation at screening deemed clinically relevant by the investigator
12. Criterion modified per Amendment 1
12.1 Criterion Removed per Amendment 2
12.2
13. Known allergies, hypersensitivity, or intolerance to talacotuzumab or decitabine or its excipients[15,16]
14. Criterion Modified per Amendment 2
14.1 Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or physical limitations that could prevent, limit, or confound the protocol-specified assessments
15. Major surgery, (eg, requiring general anesthesia) within 4 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study
Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate. In such cases, the investigator must notify the sponsor before randomization.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before 1) Cycle 1 Day 1 for Part A or 2) randomization for Part B such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

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

1. Refer to Section 8 PRESTUDY AND CONCOMITANT THERAPY for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study for Part B using an interactive web response system (IWRS). Subjects will be stratified by baseline ECOG performance status score (0-1 versus 2) and type of AML (de novo versus secondary) and then assigned randomly to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor.

After Interim Analysis #2, enrollment to the study was closed and therefore the IWRS was closed to randomization of new subjects.

Blinding

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

6. DOSAGE AND ADMINISTRATION

6.1. Dosing Schedule

6.1.1. Part A

In Part A of the study dosing will occur as per Table 2 below.

Table 2: Dosing Schedule for Part A

	Cycle 1 Talacotuzumab		All subsequent cycles									
Study Day	**1**	**2-14**	**1**	**2**	**3**	**4**	**5**	**6-7**	**8**	**9-21**	**22**	**23-28**
Decitabine (20 mg/m^2)			X	X	X	X	X					
Talacotuzumab (9 mg/kg)	X								X		X	

Cycles may be delayed due to recovery from toxicity or other causes.

6.1.2. Part B

In Part B of the study, subjects will receive study therapy according to the arm to which they are assigned. The start of each cycle is defined as the date of the first dose of decitabine. Cycles may be delayed due to recovery from toxicity or other causes. Study treatment continues until treatment failure, relapse from CR/CRi, unacceptable toxicity, death, or other reasons specified in Section 10.2.

In Arm 1, study therapy Cycle 1 will start with decitabine at a dose of 20 mg/m^2 IV administered daily for five consecutive days followed by IV treatment with talacotuzumab (at the RP2D) on Days 8 and 22 (± 24 hours) of a 28-day cycle. Subsequent cycles of study therapy will follow the same dosing schedule as Cycle 1 as outlined in Table 3.

Table 3: Dosing Schedule for Part B - Arm 1

	All treatment cycles									
Study Day	**1**	**2**	**3**	**4**	**5**	**6-7**	**8**	**9-21**	**22**	**23-28**
Decitabine (20 mg/m^2)	X	X	X	X	X					
Talacotuzumab (RP2D mg/kg)							X		X	

Subjects assigned to Arm 2 will receive decitabine at a dose of 20 mg/m^2 IV administered daily for five consecutive days. A Cycle of study therapy will be repeated every 28 days from the first dose of decitabine onwards. The dosing schedule for Arm 2 is outlined in Table 4.

Table 4: Dosing Schedule for Part B - Arm 2

	All treatment cycles					
Study Day	**1**	**2**	**3**	**4**	**5**	**6-28**
Decitabine (20 mg/m^2)	X	X	X	X	X	

Investigators should be aware that for treatment with decitabine as monotherapy or in combination, it is recommended that subjects be treated for a minimum of 4 cycles; however, a complete or partial response may take longer than 4 cycles.

Study treatment is to continue until treatment failure, relapse from CR/CRi, or death, unless discontinued early because of unacceptable toxicity. Subjects in Arm 1 may discontinue 1 of the study treatments (decitabine or talacotuzumab) because of unacceptable toxicity and continue treatment the other agent until treatment failure, relapse from CR/CRi, or death, unless discontinued early because of unacceptable toxicity.

Following Amendment 6, enrollment to the study was closed and subjects receiving talacotuzumab + decitabine should discontinue talacotuzumab treatment and may continue to receive decitabine alone, according to Principal Investigator decision and subject agreement.

Following Amendment 7 and when 270 deaths have occurred or 6 months after the last subject is enrolled (whichever occurs first), follow up of subjects and data collection will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository.

6.2. Decitabine

6.2.1. Preparation and Administration of Decitabine

Decitabine will be supplied as a lyophilized powder in a single-dose vial of 50 mg per vial. Decitabine powder should be reconstituted as outlined in the prescribing information. Decitabine will be administered at a dose of 20 mg/m^2 by continuous IV infusion over 1 hour repeated daily for 5 days at the start of each cycle. The 5-Day decitabine treatment will be repeated every 28 days.

6.2.2. Decitabine: Premedication

As outlined in the prescribing information, subjects receiving decitabine may be premedicated with anti-emetic therapies according to institutional standards.

6.2.3. Decitabine Dose Modifications

Treatment with decitabine may be delayed for up to 28 days at the discretion of the investigator, if the subject experiences disease related complications such as myelosuppression-associated complications (such as: febrile neutropenia [temperature ≥38.5°C and absolute neutrophil count <1000/µL], active viral, bacterial or fungal infection [ie, requiring intravenous anti-infectives or extensive supportive care], hemorrhage [gastrointestinal, genito-urinary, pulmonary with platelets <25000/µL or any central nervous system hemorrhage]). The treatment with decitabine may be resumed once these conditions have improved or have been stabilized with adequate treatment (anti-infective therapy, transfusions, or growth factors). If there is more than a 28-day dose delay, the subject may be permitted to continue treatment if the investigator believes it is in the best interest of the subject. Dose reduction is not recommended.

In Arm 1, if a subject discontinues decitabine because of unacceptable toxicity, they should continue treatment with talacotuzumab alone.

6.3. Talacotuzumab

6.3.1. Preparation and Administration of Talacotuzumab

Talacotuzumab will be supplied as a lyophilized product containing 100 mg of active pharmaceutical ingredient (50 mg/mL after reconstitution with 2.0 mL sterile water for injection).

The talacotuzumab dose administered will be dependent upon the subject's weight at the Day 1 assessment of each cycle. The talacotuzumab dose should be adjusted in case the subject's weight changes by >10%. Talacotuzumab will be administered as a 250 mL IV infusion over approximately 305 minutes using an infusion pump. The talacotuzumab treatment will be administered per the dosing schedule described in Section 6.1.2. Subjects should be carefully observed during talacotuzumab infusions. Trained study staff at the clinic should be prepared to intervene in case any infusion reactions occur. Resuscitation equipment and other agents necessary to treat anaphylaxis must be readily available (eg, epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, oxygen). Attention to staffing should be considered when multiple subjects will be dosed at the same time.

The rate of the talacotuzumab infusion is as follows:

First Four Cycles: Initiate the IV infusion at a rate of 10 mL/hr. In the absence of any infusion-related reaction during the first 30 minutes, increase the infusion rate to 20 mL/hr for 30 minutes, if no infusion reaction is observed during this 30 minute period, increase the infusion rate to 40 mL/hr for the next 30 minutes. If no infusion reaction is observed during this 30 minute period, increase the infusion rate to 60 ml/hr for the remainder of the infusion. The infusion rate should not exceed 60 mL/hr at any time. Subjects should be monitored for infusion reactions for one hour after completion of the talacotuzumab infusion.

Subsequent Cycles (after the first 4 cycles): If no infusion reaction is observed in the first 4 cycles, initiate the IV infusion at a rate of 40 mL/hr for 30 minutes and if no infusion-related reactions are observed during this period increase the infusion rate by 40 mL/hr every 30 minutes. The infusion rate should not exceed 150 mL/hr at any time. Subjects should be monitored for infusion reactions for 1 hour after completion of the talacotuzumab infusion.

If an infusion-related reaction is observed during the administration of talacotuzumab, then follow the procedures described in Section 6.3.4.

6.3.2. Talacotuzumab: Premedication

All subjects receiving talacotuzumab in the current study must receive premedication during the first 4 cycles, as outlined in Table 5. If no infusion-related reactions, independent of severity, are seen for 2 consecutive cycles during the first 4 cycles of talacotuzumab treatment, then premedication may be modified per investigator discretion after discussion with the Sponsor for

Cycle 5 and subsequent talacotuzumab treatments. In the event an infusion-related reaction (independent of severity) occurs in subsequent talacotuzumab treatments, premedication needs to be reintroduced. If a subject has a medical condition or clinical need that precludes complete administration of premedications at any time, notification to and discussion with the Sponsor's study physician is required.

Table 5: Premedication for Subjects Receiving Talacotuzumab

Part A and Part B – Arm 1	Infusion-related Reaction	Mandatory Premedication[2]
Cycle 1- Cycle 4		Dexamethasone 8 mg PO (or equivalent) twice per day approx. 2 days prior to infusion and approx. 3 hrs prior to infusion Methylprednisolone (100 mg IV)[1] approx. 1-2 hrs prior to infusion Acetaminophen (paracetamol) 650 – 1000 mg IV or PO approx.1 hr prior to infusion Antihistamines: diphenhydramine 25 – 50 mg IV or PO[3] and cimetidine 300 mg PO (or equivalent[4]) approx. 1 hr prior to infusion Leukotriene inhibitor (montelukast 10 mg PO, or equivalent), approx. 1-2 hrs prior to infusion
Cycle 5 + Subsequent cycles	**If Prior Event:**	Dexamethasone 8 mg PO (or equivalent) twice per day approx. 2 days prior to infusion and approx. 3 hrs prior to infusion Methylprednisolone (100 mg IV)[1] approx. 1-2 hrs prior to infusion Acetaminophen (paracetamol) 650 – 1000 mg IV or PO approx.1 hr prior to infusion Antihistamines: diphenhydramine 25 – 50 mg IV or PO[3] and cimetidine 300 mg PO (or equivalent[4]) approx. 1 hr prior to infusion Leukotriene inhibitor (montelukast 10 mg PO, or equivalent), approx. 1-2 hrs prior to infusion
	No Prior Event for 2 consecutive cycles:	Premedication may be modified per investigator discretion and after discussion with the Sponsor

[1] If methylprednisolone is not available at the institution, consult with Sponsor regarding corticosteroid selection. Dose and frequency may be increased at the discretion of the investigator.
[2] Additional doses of steroids prior to treatment with talacotuzumab may be given at the discretion of the investigator.
[3] Or similar sedating antihistamine per institutional standards; avoid the use of promethazine.
[4] For example: famotidine 20 mg (PO or IV), ranitidine 150 mg PO or 50 mg IV, or nizatidine (150 mg PO)

6.3.3. Talacotuzumab Dosing Modifications

Refer to Section 6.3.4 for details on management of infusion-related reactions.

In Part B of the study, dose reduction of talacotuzumab is not permitted and dose delay is the primary method for managing talacotuzumab-related toxicities.

A dose delay should occur if any of the following criteria is met even if the event in the opinion of the investigator is attributed to decitabine:

- Febrile neutropenia;
- Grade 3 or higher hemorrhagic event
- Toxicity that in the opinion of the investigator, requires delay.

If the dose of talacotuzumab is delayed by more than 3 days, then the dose should be skipped. Administration may resume at the next planned dosing date. A missed dose will not be made up.

If there is more than a 28-day delay between doses, then the subject may be permitted to continue treatment if the investigator believes it is in the best interest of the subject. However, this must be approved by the Sponsor.

In Arm 1, if a subject discontinues talacotuzumab because of unacceptable toxicity, they should continue treatment with decitabine alone.

If a dose delay occurs, then pharmacokinetic and biomarker assessments should be performed on the actual administration day of talacotuzumab, not on the original scheduled administration day.

Dose reduction in Part A: Stepwise dose reductions described in the table below are permitted if requested and approved by the sponsor in the event of unacceptable toxicity defined as non-hematologic Grade ≥ 3 AE or Grade 4 hematologic toxicity lasting more than 14 days and not responsive to treatment and/or supportive care.

	Talacotuzumab dosing
0	9 mg/kg
-1	6 mg/kg
-2	3 mg/kg

6.3.4. Management of Potential Hypersensitivity/ Infusion-related Reactions

Subjects who experience treatment emergent adverse events during the IV infusion of talacotuzumab must be treated according to the investigator's judgment and best clinical practice. The following guidelines may apply:

- Subjects should be treated with acetaminophen, H1-antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require H1-antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.

- In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events), or anaphylactic reaction, talacotuzumab should be discontinued and no additional talacotuzumab should be administered to the subject.

6.3.4.1. Guidelines for the Interruption of Talacotuzumab Infusion due to Infusion-related Reaction

Infusion-Related Events of Grade 1 or Grade 2

If the investigator assesses a TEAE to be related to the talacotuzumab infusion, then the infusion should be paused. When the subject's condition is stable, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion but should not exceed 60 mL/hr for Cycles 1 to 4 and 150 mL/hr for subsequent cycles at any time.

If the subject experiences a Grade 2 or higher event of laryngeal edema or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from the onset, then the subject must be withdrawn from treatment.

Infusion-Related Reactions of Grade 3 or Higher

For infusion-related TEAEs that are Grade 3, the talacotuzumab infusion must be stopped, and the subject must be observed carefully until resolution of the TEAE or until the intensity of the event decreases to Grade 1 or baseline, at which point the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion but should not exceed 60 mL/hr for Cycles 1 to 4 and 150 mL/hr for subsequent cycles at any time. If the intensity of the TEAE returns to Grade 3 after restart of the infusion, then the procedure described in this section may be repeated at the investigator's discretion.

For infusion-related TEAEs that are Grade 4, the infusion should be stopped and treatment with talacotuzumab will be discontinued for that subject.

7. TREATMENT COMPLIANCE

Decitabine and talacotuzumab will be administered as IV infusions by qualified staff and the details of each administration will be recorded in the eCRF. Additional details are provided in the Site Investigational Product Procedures Manual.

Following Amendment 7 and when 270 deaths have occurred or 6 months after the last subject is enrolled (whichever occurs first), the eCRFs will be closed.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapies administered up to 28 days before the first dose of study drug (Part A) or 28 days before randomization (Part B) must be recorded at screening. Prior systemic therapies for MDS or MPN administered before signing of the informed consent should be collected at screening. Concomitant therapies must be recorded throughout the study beginning with signing of the

Informed Consent Form and continuing until 30 days after the last dose of study drug. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Following Amendment 7 and when 270 deaths have occurred or 6 months after the last subject is enrolled (whichever occurs first), follow up of subjects and data collection will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository.

8.1. Permitted Medications and Supportive Therapies

All concomitant medications for medical conditions other than AML are permitted, as clinically indicated. All supportive therapies, other than anticancer treatment needed for the management of subjects enrolled in this study, are encouraged.

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

- Short-term (<3 days) treatment with low doses of systemic corticosteroids when medically necessary for the control of acute symptoms or for premedication of talacotuzumab;
- Prophylactic antibacterial, antifungal, or antiviral agents need to be used per institutional guidelines;
- Growth factors are strongly recommended to 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 subjects. Growth factors need to also be used to prevent treatment delay due to neutropenia.
- Red blood cell and platelet transfusions per institutional guidelines.

8.2. Prohibited Therapies

The following medications are prohibited during the study:

- Concurrent systemic corticosteroids except for short-term treatment and mandatory premedication;
- Plasmapheresis, cytoreduction by hydroxyurea or other concurrent anticancer therapy. Of note: treatment with hydroxyurea and plasmapheresis has to be discontinued prior to start of study therapy;
- Any investigational agent; and
- Any live attenuated vaccination.

8.3. Subsequent Antineoplastic Therapies

Administration of any other antineoplastic therapy, for reasons other than treatment failure (defined in Section 9.2.1.1) or relapse from CR/CRi, is strongly discouraged until treatment

failure or relapse is established. After treatment failure or relapse is established, subsequent therapy is permitted at the investigator's discretion. Subsequent therapy (including start date, end date, and best response) should be documented in the appropriate section of the eCRF.

9. STUDY EVALUATIONS

Following Amendment 6, which incorporated the IDMC's recommendations to close enrollment to the study and discontinue talacotuzumab treatment for subjects receiving talacotuzumab + decitabine and offer to continue decitabine alone, all subjects will continue to be followed for survival and subsequent anti-cancer therapy. During the treatment phase with decitabine, subjects will be monitored for serious adverse events.

Following Amendment 7 and when 270 deaths have occurred or 6 months after the last subject is enrolled (whichever occurs first), follow up of subjects and data collection will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository.

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules: Tables 1A, 1B, 1C, 1D, 2A, and 2B summarize the frequency and timing of efficacy, pharmacokinetic, immunogenicity, pharmacodynamic, biomarker, pharmacogenomic, patient-reported outcomes, and safety measurements applicable to this study. Every effort should be made to keep subjects on the study schedule as planned from Study Day 1. At each visit, study assessments should be completed before study drug administration. All PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions but prior to and on the day of the actual study drug administration.

Post-baseline disease evaluations may be conducted ±7 days from the scheduled visit date, if necessary. At the following visit, the subject should return to the original planned schedule. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Medical resource utilization data will be collected. Refer to Section 9.8 for details.

Assuming a study duration of 6 cycles, the total blood volume to be collected from each subject will be approximately 336 mLs for subjects participating in Part A, 541 mLs for subjects participating in Part B Arm 1 (decitabine + talacotuzumab) and 387 mLs for subjects participating in Part B Arm 2 (decitabine only). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

The signed informed consent form (ICF) must be obtained before any study-specific procedures are performed. The Screening Phase begins when the first screening assessment is conducted (that was not performed as part of the subject's standard of care). During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in Time and Events Schedule Tables 1A and 1B. Screening procedures will be performed within 28 days before first dose (Part A) or within 28 days before randomization (Part B).

9.1.3. Open-Label Treatment Phase

Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedule Tables 1A, 1B, and 1C. For Part A, treatment will start on Day 1 with an IV infusion of talacotuzumab and proceed as described in Section 6.1. Subjects will continue on study and receive open label talacotuzumab in combination with decitabine in Part A until treatment failure, relapse from CR/CRi, unacceptable toxicity, death or other reasons specified in Section 10.2.

For Part B, treatment with study drug should start within 3 days after randomization and continue until treatment failure, relapse from CR/CRi, unacceptable toxicity, death, or other reasons specified in Section 10.2.

All subjects in Part A and Part B will be closely monitored for adverse events, laboratory abnormalities, and disease status. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If treatment failure or relapse from CR/CRi occurs, then the subject will complete the End-of-Treatment Visit and enter the Follow-up Phase. Subjects randomized into the decitabine + talacotuzumab arm can discontinue 1 drug (decitabine or talacotuzumab); while continuing treatment with the other drug.

End of Treatment

All subjects should have an End-of-Treatment Visit, unless a subject withdraws consent for study participation or is lost to follow up. The End-of-Treatment Visit is to occur within 30 days (+/- 7 days) after the last dose of study drug. Every effort should be made to conduct the End-of-Treatment Visit before the subject starts subsequent treatment.

9.1.4. Follow-up Phase

The Follow-up Phase will begin once a subject has completed the End-of-Treatment Visit. Subjects who discontinue before treatment failure or relapse from CR/CRi must continue to have disease evaluations according to the Time and Events Schedule Tables 1A, 1B, and 1C. Subjects with unresolved drug-related adverse events of Grade 3 or higher as well as ongoing drug-related serious adverse events (SAEs) will be followed until event resolution. After treatment failure or relapse is documented, only subsequent anticancer therapy, concomitant therapy to treat a continuing drug-related adverse events (AE) ≥ Grade 3 or serious adverse event (SAE), survival status, and other malignancies will continue to be collected. If this information is obtained via telephone contact, then written documentation of the communication must be available for

review in the source documents. If the subject has died, then the date and cause of death will be collected and documented on the eCRF.

End of Study

The end of study data collection is defined as when 270 deaths have occurred or 6 months after the last subject is enrolled, whichever occurs first. At that time, follow up of subjects will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository as described under Amendment 7.

9.1.5. Disease Evaluation and Clinical Cutoff

Disease evaluations will be performed for each subject per the Time and Events Schedule Tables 1A and 1B until treatment failure, relapse from CR/CRi, or until the study has reached the clinical cutoff for OS or EFS, whichever occurs first. If the study continues enrollment to 400 subjects then the clinical cut-off for the final analysis of OS is when 270 subjects have died. If study enrollment stops with approximately 120 subjects, the clinical cut-off for the final analysis of EFS is when 90 EFS events have occurred. Enrollment was terminated after Interim Analysis #2 and the study will end 6 months after the last subject was enrolled.

9.2. Efficacy

9.2.1. Evaluations

Disease assessments based on bone marrow evaluations, peripheral blood counts, and clinical presentation will be conducted per the Time and Events Schedule Tables 1A, 1B, and 1C at the local laboratory. Cytogenetics will be evaluated at the local site.

In Part B, bone marrow aspirates will be collected every 2 cycles. All treatment decisions will be based on local assessments. Additionally, slides will be sent to a central laboratory for analysis of the percentage of leukemic blast cells. A portion of the bone marrow aspirate specimen will also be sent in the appropriate medium for MRD status. Bone marrow biopsy material is not required, unless an aspirate sample cannot be obtained (dry tap).

9.2.1.1. Disease Status

Subjects will be assessed for disease status according to the "Response Criteria in AML"[9] with a modification by the Sponsor for treatment failure (Table 6). The modification is necessary because the original criteria were intended for evaluation of standard induction therapy with 3 days of an anthracycline and 7 days of cytarabine (3+7) or therapies of comparable intensity.

If treatment failure is suspected due to clinical indications or increased peripheral blast counts, then a bone marrow sample must be obtained to confirm treatment failure as defined below. 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 treatment failure for the subject.

For this study, treatment failure is defined as >25% absolute increase in the bone marrow blast count from baseline to the present assessment (eg, from 20% to 46%) on bone marrow aspirate (or biopsy in case of dry tap).

Stable disease is defined as response that does not qualify for a complete or partial response and does not meet the criteria for treatment failure.

The sponsor must be notified before subjects discontinue study treatment. Before subjects discontinue the Treatment Phase due to treatment failure or relapse from CR/CRi, sites will document treatment failure 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 subjects, the Sponsor should be informed as soon as treatment failure or relapse from CR/CRi is confirmed. Discontinuation criteria for all subjects must be reviewed and confirmed by the Sponsor prior to discontinuation.

Based on investigator's disease assessments across all cycles of treatment, overall best response during the entire study will be derived by the Sponsor. For an overall best response of stable disease, disease stabilization must have lasted for at least 8 weeks.

Table 6: Response Assessments

Category	Definition
Complete response (CR)[1]	Bone marrow blasts <5%; absence of 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); independence of red cell transfusions
CR with incomplete recovery (CRi)[2]	All CR criteria except for residual neutropenia (<1.0 × 10^9/L [1000/µL]) or thrombocytopenia (<100 × 10^9/L [100 000/µL])
Morphologic leukemia-free state[3]	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial response (PR)	Relevant in the setting of Phase 1 and 2 clinical trials only; 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%
Cytogenetic CR (CRc)[4]	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)[5]	No standard definition; depends on molecular target
Relapse[6]	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease
Treatment failure[7]	>25% absolute increase in the bone marrow blast count from baseline to the present assessment (eg, from 20% to 46%) on bone marrow aspirate (or biopsy in case of dry tap)
Stable disease[8]	Does not qualify for a complete or partial response and has no evidence of treatment failure.

Source: Dohner 2010[9] with modification by Sponsor for treatment failure
Definitions of response criteria are based primarily on those given by Cheson 1990.[5]
[1] All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help

to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

[2] The criterion of CRi is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved in the cycle of the entire treatment plan. In these instances, the overall response rate should include CR and CRi patients. Some patients may not achieve complete hematologic recovery upon longer observation times.

[3] This category may be useful in the clinical development of novel agents within phase 1 clinical trials, in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.

[4] Four studies showed that failure to convert to a normal karyotype at the time of CR predicts inferior outcome.

[5] As an example, in core binding factor (CBF) AML low-level PCR-positivity can be detected in patients even in long-term response. Normalizing to 104 copies of ABL1 in accordance with standardized criteria, transcript levels below 12 to 10 copies appear to be predictive for long-term response.

[6] In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

[7, 8] Modified by Sponsor to meet the need for subjects in this study who are not candidates for conventional intensive induction chemotherapy.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

For all subjects participating in the study, pharmacokinetic samples to determine plasma concentrations of decitabine and serum concentrations of talacotuzumab will be obtained according to the Time and Events Schedule Tables 2A and 2B.

Venous blood samples (approximate 7.5 mL per sample) will be collected to determine serum concentration of talacotuzumab and the serum will be divided into 4 aliquots of approximate equal volume (1 aliquot for pharmacokinetic analysis, 1 aliquot for antibodies to talacotuzumab analysis [when appropriate], and 2 aliquots as backup). If needed, samples collected for determining serum concentrations of talacotuzumab in this study may be used for determining immunogenicity, further characterization of immunogenicity, such as the ability of anti-drug antibodies to neutralize the effect of talacotuzumab, address questions about drug characteristics that may arise at a later time point, or evaluation of safety or efficacy aspects that address concerns arising during or after the study period. Venous blood samples (approximate 0.5 mL per sample) will be collected to determine plasma concentration of decitabine. Genetic analyses will not be performed on these samples, and subject confidentiality will be maintained.

The exact dates and times of blood sampling must be recorded. Refer to the Laboratory Manual for sample collection, handling, and shipping requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the Laboratory Manual.

9.3.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of talacotuzumab and generation of antibodies to talacotuzumab (immunogenicity) using validated immunoassay methods by or under the supervision of the sponsor's bioanalytical facility as indicated by the Time and Events

Schedule Tables 2A and 2B. If needed, interim analyses of the serum talacotuzumab concentrations from Part A may be conducted. All bioanalytical results from the interim analysis will be considered final and these samples will not be re-assayed at the end of the study.

Plasma samples will be analyzed to determine the concentration of decitabine using a validated LC/MS/MS method by or under the supervision of the sponsor's bioanalytical facility. The complete bioanalytical report, describing the assay methodologies and results, will be included as an appendix to the pharmacokinetic report which is contained within the integrated study report.

9.3.3. Pharmacokinetic Parameters

Plasma concentrations of decitabine and serum concentrations of talacotuzumab will be measured and resulting concentration over time data will be summarized by treatment. Population PK models will be explored and developed if data are sufficient from this study. If sufficient data are available, the pharmacokinetic parameters such as the ones listed below for talacotuzumab may be calculated.

$AUCt_1.t_2$	Area under the concentration-time curve between time t_1 and t_2
CL	total systemic clearance of drug after IV administration
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
V	volume of distribution

Pharmacokinetic samples to determine the plasma concentration of decitabine and the serum concentration of talacotuzumab will be obtained from all applicable subjects in the study as described in Time and Events Tables 2A and 2B.

9.3.4. Immunogenicity Assessments

For all subjects in Part A and those randomized to receive decitabine + talacotuzumab in Part B, venous blood samples will be drawn to assess the generation of antibodies to talacotuzumab (immunogenicity), as specified in the Time and Events Schedule Tables 2A and 2B. Additionally, blood samples to assess immunogenicity should be collected at the final visit for subjects who discontinue treatment or withdrawn from the study. Subjects who discontinue treatment in Part B will also be asked to return for an immunogenicity evaluation during the Follow-up Phase.

All samples collected for immunogenicity analysis will be evaluated for talacotuzumab serum concentration to ensure appropriate interpretation of immunogenicity data. At each time point, immunogenicity and serum talacotuzumab concentration analyses will be performed on aliquots from the same blood draw and no additional sampling is required. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document.

Serum samples will be screened for antibodies binding to talacotuzumab and serum titer will also be determined from confirmed positive samples using validated assay methods by or under the supervision of the sponsor. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated.

Any time an infusion-related reaction is observed or reported during the study, a blood sample should be drawn for determination of antibodies to talacotuzumab. Talacotuzumab serum concentration will also be determined from the same infusion-related reaction sample for the purpose of interpreting immunogenicity data. These samples will be stored and evaluated if deemed necessary. If the infusion-related reaction results in treatment discontinuation, then subjects should undergo all scheduled safety and efficacy evaluations. Samples collected for the analysis of talacotuzumab immunogenicity/serum concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers by the sponsor or sponsor's designee.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

If sufficient data are available, pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of talacotuzumab 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.

9.5. Biomarkers

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed if, during or at the end of the study, it becomes clear that the analysis will have no scientific value, or if there are not enough samples or not enough 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. Samples for biomarker evaluations will be collected as specified in the Time and Events Schedule Tables 2A and 2B.

9.5.1. Assessment of Pharmacodynamic Markers (Part A and Part B)

Changes in cell numbers of cellular biomarkers (basophils, pDCs, monocytes, NK cells and eosinophils) as well as CD123 expression and receptor occupancy will be measured by flow cytometry or other similar technologies.

9.5.2. Assessment of CD123 Expression (Part B)

CD123 expression and density will be determined in AML blasts and LSCs in bone marrow and blood by flow cytometry at a central laboratory and may be compared with other methods such as reverse transcriptase – quantitative polymerase chain reaction (RT-qPCR), CD123 expression may be followed when bone marrow aspirates or blood samples are obtained for clinical assessment of CR or CRi and upon treatment failure or relapse from CR/CRi, and at End-Of-Treatment to evaluate changes in CD123 expression in the myeloid blast and LSC population with talacotuzumab treatment (Time and Events Schedule Table 1B and 1C).

9.5.3. Minimal Residual Disease Assessment (Part B)

Minimal residual disease assessments will be performed on bone marrow aspirates and may be compared with assessments in whole blood collected at time points as specified in the Time and Events Table 1B. The objective is to compare MRD in subjects from both arms who achieve a CR or CRi response. Minimal residual disease negativity is defined as less than 1 blast or leukemic stem cell in 10,000 leukocytes (MRD level $<10^4$). Flow cytometry will be utilized as the primary method of MRD analysis, and when available, may be compared to other molecular approaches such as PCR or next-generation sequencing (NGS) of specific genomic abnormalities.

9.5.4. Immunophenotyping (Part B)

Bone marrow aspirates (as available per Time and Events Schedule Table 1B) or whole blood may be utilized for immunophenotyping (performed by flow cytometry or mass cytometry/CyTOF) which includes analyses of NK cells, T cells, and B cells as well as other potential immune cell subpopulations. The main mechanism of action of talacotuzumab is ADCC through NK cell activation; therefore, NK cell counts and activation will be assessed by flow cytometry (Time and Events Schedules Tables 1B, 2A, and 2B). Patients receiving decitabine will be analyzed pre- and post-decitabine treatment for NK cell number and activity in an attempt to address the effect of decitabine on NK cell function (Time and Events Schedules Tables 2A and 2B). Subjects in Part A will only be assessed for NK cell activity and cell numbers by flow cytometry (Time and Events Schedule Table 2A). To investigate whether an immune fitness signature can be developed utilizing either flow cytometry or genomic profiling, whole blood samples may also be subjected to RNA profiling (RNA-seq, gene expression profiling), or methylation assessment to evaluate novel technologies for immune profiling in bone marrow and whole blood, and to compare these methodologies to standard flow cytometry or CyTOF. These assessments will be evaluated for association with clinical outcome.

9.5.5. Cytokine Analysis

Samples (blood) for cytokine analysis will be collected as described in the Time and Events Schedule 2B.

Infusion-related reactions occur with the administration of talacotuzumab. Cytokine analysis will be performed to determine the association of cytokines with infusion-related reactions and to help gain an understanding of the mechanism of these reactions.

9.6. Pharmacogenomic (DNA and RNA) Evaluations (Part B)

DNA or RNA samples will be used for research related to talacotuzumab (CSL362) and/or decitabine or AML. They may also be used to develop tests/assays related to talacotuzumab (CSL362) and/or decitabine and AML. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome in relation to talacotuzumab or AML clinical endpoints.

More specifically, myeloid specific genomic profiling may be done employing a panel of genes with known myeloid mutations such as NPM1, FLT3-ITDD, DNMT3a, TET2, IDH1/2 that will

be sequenced and analyzed in correlation to prognosis and response to talacotuzumab or decitabine treatment. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.

Gene expression and DNA methylation analyses may be analyzed on bone marrow aspirates and/or peripheral blood samples at baseline and post decitabine exposure if deemed necessary to evaluate the decitabine effect in combination with talacotuzumab. Single nucleotide polymorphism (SNPs) associated with ADCC or NK-cell activity may be evaluated if warranted based on additional clinical data.

9.7. Patient-reported Outcomes

9.7.1. FACT-Leu

The FACT-Leu, a self-administered PRO measure, will be used in this study. It will enable the evaluation of a subject's perceptions of health-related quality of life.

The FACT-Leu is a 44-item, self-reported leukemia-specific measure that is used to quantitatively assess an individual's perception of how the disease affects their day-to-day life. It includes 5 subscales, ie, physical well-being, social/family well-being, emotional well-being, functional well-being, and leukemia-specific concerns. All FACT-Leu subscale and aggregated scores showed high internal consistency and high test-retested reliability.[4] A sample of the FACT-Leu containing representative questions is provided in Attachment 1.

9.7.2. EQ-5D-5L

The EQ-5D-5L is a generic measure of health status. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effective analyses. The EQ-5D-5L is a 5 item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[7,22] The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. A sample of the EQ-5D-5L that contains representative questions is provided in Attachment 2.

9.8. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all subjects 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:

- 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)

9.9. Safety Evaluations

Details regarding the Independent Data Monitoring Committee are provided in Section 11.12.

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 endpoint is reached. The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule Tables 1A, 1B, 1C, and 1D:

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) from the time a signed and dated informed consent form is obtained. Adverse events will be reported until 30 days after the last dose of study drug. During the Follow-up Phase, any adverse events of Grade 3 or higher that are considered related to study drug, as well as related serious adverse events, should be followed until resolution or until a clinically stable endpoint is reached. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Following Amendment 7 and when 270 deaths have occurred or 6 months after the last subject is enrolled (whichever occurs first), follow up of subjects and data collection will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected as specified in the Time and Events Schedule Tables 1A and 1B and 1C. Additional clinical laboratory tests may be performed as indicated by the overall clinical condition of the subject or if abnormalities warrant more frequent monitoring. Hematology and serum chemistry laboratory evaluations may be repeated as clinically indicated. 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. Screening laboratory results must be available to the investigator for evaluation before the first dose of study drug on Day 1 of Cycle 1.

The following tests will be performed by the local laboratory:

- Hematology Panel

  -hemoglobin
  -absolute white blood cell (WBC) count
  -platelet count
  -absolute monocyte count
  -absolute basophil count

-absolute eosinophil count
-absolute neutrophil count
-absolute lymphocyte count
- peripheral blast count

- Coagulation:

  -activated partial thromboplastin time (aPTT)
  -International normalized ratio (INR) or prothrombin time (PT)

- Serum Chemistry Panel

-sodium	-aspartate aminotransferase (AST)
-potassium	-alanine aminotransferase (ALT)
-magnesium	-alkaline phosphatase
-creatinine	-calcium
-total bilirubin	-blood urea nitrogen (BUN)
-phosphate	-uric acid

- Serum β-hCG or urine pregnancy testing for women of childbearing potential only (screening only) or if clinically indicated or required by local regulations.

Electrocardiogram (ECG)

Electrocardiogram will be performed for all subjects during screening as indicated in the Time and Events Tables 1A and 1B. Abnormalities noted at screening should be included in the medical history. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects 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, then the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

In Part A, QTcF will be assessed at the time of screening and in the Open-Label Treatment Phase if clinically required. If QTcF is >470 milliseconds, refer to the Time and Events Schedule Tables 1A,1B, and 1C for additional assessment procedures.

In Part B, ECG monitoring for subjects in Arm 1 will occur during screening and on Cycle 1 Day 8 and Day 22 after the talacotuzumab IV infusion, then every 2 cycles thereafter on Day 22 after the talacotuzumab IV infusion and at EOT. For subjects in Arm 2, ECG monitoring will occur during screening and on Cycle 1 Day 5 after the decitabine IV infusion and then every 2 cycles thereafter on Day 5 after the decitabine IV infusion and at EOT.

Multi Gated Acquisition (MUGA) Scan/ Echocardiography

Baseline left ventricular ejection fraction (LVEF) measured by (MUGA or echocardiogram) must be assessed and be within institutional limits for subjects to be eligible for this study and may be repeated throughout the study when clinically indicated and at EOT. When the exam is repeated, the same measurement modality should be used.

Vital Signs

Temperature, heart rate, blood pressure will be recorded according to the Time and Events Schedule Tables 1A and 1B. 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).

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 Time and Events Schedule Tables 1A, 1B, and 1C. Any changes that are clinically significant will be recorded on the AE page. Height will be measured at Screening only; weight will be measured prior to the start of each cycle and at the EOT.

ECOG Performance Status

The ECOG Performance Status scale will be used to grade changes in the subject's daily living activities. The ECOG Performance Status scale is provided in Attachment 3. The frequency of ECOG Performance Status assessment is provided in the Time and Events Schedule Tables 1A and 1B.

9.10. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. When applicable, blood samples should be collected from the arm contralateral to the drug infusion arm. 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. Refer to the Time and Events Schedule Tables 2A and 2B for the timing and frequency of all sample collections.

For samples collected for the central laboratory, sample dates and times must be recorded on the laboratory requisition form. Further 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.

10. DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has finished all protocol-specified procedures, has not been lost to follow up, and has not withdrawn consent for study participation before the end of study data collection. In addition, subjects who die prior to the end of study data collection will be considered to have completed. Subjects in the Follow-up Phase will be considered to have completed the study when the end of study data collection has been reached (270 deaths have occurred or 6 months after the last subject is enrolled, whichever occurs first; see Section 9.1.4). Following Amendment 7, follow up of subjects and data

collection will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository.

10.2. Discontinuation of the Treatment Phase

If a subject's study treatment must be discontinued before the end of the treatment regimen, then this will not result in automatic withdrawal of the subject from the study. A subject's participation in the Treatment Phase will be discontinued if any of the following occur:

- The subject experiences treatment failure (defined in Section 9.2.1.1) or relapse from CR/CRi;
- The subject experiences unacceptable toxicity (In Arm 1, subjects may discontinue 1 drug while continuing treatment with the other drug);
- The subject experiences a severe infusion reaction with cardiovascular collapse;
- The subject initiates treatment with a prohibited medication;
- The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an adverse event) it is in the best interest of the subject to discontinue treatment;
- The subject becomes pregnant; or
- The subject (or the subject's legally acceptable representative) withdraws consent for administration of study treatment.

Before subjects discontinue the Treatment Phase due to treatment failure or relapse from CR/CRi, sites will document treatment failure 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 subjects, the Sponsor should be informed as soon as treatment failure or relapse from CR/CRi is confirmed and all treatment discontinuations will be reviewed for approval by the Sponsor.

After discontinuation from the Treatment Phase, all subjects in both treatment groups should have an End-of-Treatment Visit and enter the Follow-up Phase. Follow-up assessments should continue as specified in the Time and Events Schedules (Tables 1A,1B, 1C, and 1D).

10.3. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- The study investigator or Sponsor, for any reason, stops the study or stops the subject's participation in the study

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study, then the assessments outlined in the End-of-Treatment Visit should be obtained.

10.4. Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). 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.

11. STATISTICAL METHODS

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.

11.1. Subject Information

The primary analysis population will be the all-randomized population, which will include all subjects in Part B. Safety will be evaluated for all subjects who have received at least 1 dose of study drug in Part A or Part B. The pharmacokinetic analyses will be performed on the pharmacokinetic evaluable population. Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, and range. Categorical variables will be summarized using frequency tables.

11.2. Interim and Final Analyses

Safety reviews will be performed in Part A and Part B. The safety assessments by the Study Evaluation Team (SET) in Part A will occur prior to the initiation of Part B. This will include available PK and PD data from both single agent talacotuzumab and the combination of decitabine + talacotuzumab. In addition, a safety review by the IDMC of the accumulative data will be performed when approximately 20 subjects (10 subjects from each arm) have been enrolled in Part B and followed for at least 1 month to assess the safety and tolerability of the combination treatment. This review will also include all safety, PK, and PD data available from Part A.

Part B of the study includes an interim analysis based on response rates of CR and CR+CRi that will occur after approximately 80 subjects (40 subjects per arm) have been randomized and followed for at least 4 months. The results of this interim analysis will be used to guide if the study continues enrollment to the pre-specified 400 subjects or stops enrollment. Enrollment will continue during the interim analysis; it is estimated that approximately 120 subjects will have been randomized by the time the results of the first interim analysis are available.

The statistical criteria to guide the decision making will be based on the difference (Δ) in response rate between the 2 treatment arms (decitabine + talacotuzumab minus decitabine alone) as the following:

- If ΔCR ≥15% or Δ(CR+CRi) ≥25%, then the study may continue enrollment to 400 subjects;
- If ΔCR <15% and Δ(CR+CRi) <25%, then the study may stop enrollment at approximately 120 subjects.

The IDMC will use the above response rate criteria as well as the totality of the data to guide the recommendation regarding enrollment continuation to 400 subjects or stopping enrollment at this interim analysis. The final decision will be made by the Sponsor based on the IDMC recommendation, totality of the data, and other development considerations.

If the study continues enrollment to 400 subjects, then the overall Type 1 error of 0.05 (2-sided) will be allocated between the primary endpoints of CR rate and OS using a gate-keeping procedure as described below:

- There will be a formal statistical testing for superiority for CR at the interim analysis of 80 subjects with 2-sided α=0.001. The final analysis of CR (in terms of formal statistical hypothesis testing) will take place after 160 subjects have been randomized and followed for 4 months (to occur at the same time as the 1st interim analysis of OS) with 2-sided α=0.009. The study and collection of response data continue after the final CR analysis regardless of the outcome of the analysis.
- Overall 2-sided α=0.04 for OS; and if the final analysis of CR achieves statistical significance, then α=0.009 allocated to this CR analysis can be reclaimed by OS analysis, ie, OS can be tested at the overall level of 0.049.
- The 2 interim analyses and final analysis for OS will utilize the O'Brien-Fleming α-spending procedure.

If the study stops enrollment after the first interim analysis, then the clinical cut-off will be when 90 EFS events have occurred. The analyses of these 120 subjects will be exploratory with EFS as the primary outcome of interest.

The overall statistical inference of the study can be summarized as in Table 7.

Table 7: Overall Statistical Inference

Enrollment, No. of Subjects	Analysis	Clinical Cutoff	2-Sided α
40 subjects per arm	Interim analysis of CR and CR+CRi to determine enrollment continuation	4 months after 40 subjects per arm are randomized	0.001
Continue to approx. 400	CR final analysis	4 months after 160 subjects are randomized	0.009

	OS interim analysis No.1	At the time of final CR analysis	0.0002
	OS interim analysis No.2	180 deaths	0.0088/0.0116[a]
	OS final analysis	270 deaths	0.0372/0.0454[a]
Stop with approx. 120	EFS final analysis[b]	90 EFS events	NA

[a] If CR final analysis reaches statistical significance
[b] Exploratory without formal statistical hypothesis testing

11.3. Sample Size Determination

Part A:

Approximately 6 subjects will be enrolled in Part A of the study in order to confirm the RP2D of talacotuzumab for Part B.

Part B:

The first interim analysis to guide the decision for study continuation will occur after approximately 80 subjects (40 subjects per arm) have been randomized and followed for at least 4 months; the operating characteristics of the criteria are shown in Table 8.

Table 8: Study Continuation Decision Rule, Operating Characteristics

Sample size	40/arm
Enrollment may continue to approximately 400 subjects	ΔCR ≥15% **or** Δ(CR+CRi) ≥25%
Enrollment may stop with approximately 120 subjects	ΔCR <15% **and** Δ(CR+CRi) <25%
False positive error rate[a]	0.04
False negative error rate[b]	0.10

[a] Decision for enrollment to approximately 400 subjects, assuming true effect of decitabine alone and decitabine + talacotuzumab are the same: CR=15%, CR+CRi=25%
[b] Decision for stopping enrollment with approximately 120 subjects, assuming true effect of decitabine alone: CR=15%, CR+CRi=25%, and true effect of decitabine + talacotuzumab: CR=40%, CR+CRi=55%
Δ=difference in response rate, decitabine + talacotuzumab minus decitabine alone

If the study continues enrollment to 400 subjects, both primary endpoints (CR rate and OS) will be powered for 80% with overall α allocation of 0.01 and 0.04, respectively (Table 9).

If the study stops enrollment after the first interim analysis, it is expected that approximately 120 subjects would have been randomized to the study. In this case, the primary focus will be exploratory to assess if there is a clinically relevant improvement in EFS for decitabine + talacotuzumab-treated subjects compared with subjects treated with decitabine alone. Assuming median EFS of 4 months for the decitabine alone arm, an improvement of 2.8 months in the talacotuzumab + decitabine arm (or hazard ratio HR=0.59) is considered clinically meaningful. For this purpose, 90 EFS events will provide 80% power to rule out a HR=1.0 (no difference in EFS between the 2 treatment arms) using a 90% confidence interval. If 120 subjects are recruited in 15 months, it is estimated that 90 EFS events will occur 5 months after the last subject is randomized.

Overall power and sample size determinations are summarized in Table 9.

Table 9: Sample Size Determination

Endpoint(s)	Effect Size, Decitabine + Talacotuzumab vs. Decitabine alone	Power	Overall 2-side α	Total No. of Events	Total Sample Size
Primary: CR Rate	40% vs. 15%	80%	0.01		160
Primary: OS	Median 11.4 vs. 8.0 months Hazard ratio=0.70	80%	0.04	270	400
Secondary: EFS	Median 6.8 vs.4.0 months Hazard ratio=0.59	80%	90% CI[a]	90	120

[a] If enrollment stops with approximately 120 subjects, analysis of EFS is exploratory with hazard ratio estimate and corresponding 90% confidence interval (CI).

11.4. Efficacy Analyses

Kaplan-Meier estimates of time to events, including OS and EFS will be presented, along with a stratified (by baseline ECOG performance status and type of AML) log-rank test comparing the 2 treatment arms. Median OS along with corresponding 95% confidence intervals (CIs) will be obtained from the Kaplan-Meier estimates. Cox's regression (stratified by baseline ECOG performance status and type of AML) will be applied to obtain the hazard ratio estimate and the corresponding 95% CI. Additional Cox's regression may be performed to include appropriate baseline prognostic variables.

Number and percent of subjects who have CR, CR+CRi, and CR plus MRD negative CRi will be calculated and compared between the 2 treatment arms using Fisher's exact test. Time to response and duration of response will also be summarized for subjects who have CR, CR+CRi, and CR plus MRD negative CRi.

Descriptive analysis will be performed for RFS.

Statistical analyses will be performed for all randomized subjects, as well as for subgroups defined by important baseline or disease characteristics, including CD123 status. Additional efficacy analyses may be performed to include appropriate data from Part A.

11.5. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population, defined as subjects who have received at least 1 dose of talacotuzumab or decitabine and have at least 1 post-infusion sample available.

Data will be listed for all subjects with available talacotuzumab or decitabine concentrations. Subjects 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 agent). All analyte concentrations below the lowest quantifiable concentration and any missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Descriptive statistics, including mean, standard deviation, coefficient of variation (%CV), median, minimum, and maximum, will be used to summarize decitabine plasma concentrations and talacotuzumab serum concentrations at each sampling time point. If appropriate, pharmacokinetic parameters of talacotuzumab such as C_{min}, $C_{max,}$ $AUCt_1$-t_2, CL, and V may be calculated. Graphical exploration of data may be performed if deemed useful.

Population PK analysis of decitabine and talacotuzumab will be explored. If sufficient data are available, then population pharmacokinetic analysis of plasma concentration x time data of decitabine or serum concentration x time data of talacotuzumab will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other studies to support a relevant structural model. In addition, available subject characteristics (eg, demographics, laboratory data, etc.) may be tested as potential influential covariates affecting PK parameters. If the population pharmacokinetic analysis is conducted, then details will be given in a population pharmacokinetic analysis plan and the results of the analysis will be presented in a separate report.

11.6. Immunogenicity Analyses

The incidence of antibodies to talacotuzumab (immunogenicity) will be summarized for all subjects who receive at least 1 dose of talacotuzumab and have appropriate samples for detection of antibodies to talacotuzumab.

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

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

11.7. Pharmacokinetic/Pharmacodynamic Analyses

If sufficient data are available, then the relationship between serum concentrations of talacotuzumab or plasma concentrations of decitabine, and PD markers, biomarkers or endpoints of clinical efficacy could be explored using population approaches (eg, non-linear mixed effects approaches). Details and results of such analysis will be presented in a separate report.

11.8. Biomarker Analyses

Biomarker studies are designed to identify markers predictive of response (or resistance) to talacotuzumab. Analyses will 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 of baseline expression levels or changes in expression levels with clinical parameters will identify responsive (or resistant) subgroups in addition to immune cells, genes and pathways attenuated following treatment with talacotuzumab.

Basophils and pDCs, as potential pharmacodynamic measures, will be listed, tabulated, and where appropriate, plotted. Subjects may be grouped by cohort, dose, or clinical response. Data from CD123 expression will be used as prognostic factors for clinical outcomes to explore if potential thresholds can be established for future subject selection. Results of biomarker and pharmacodynamic 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.

11.9. Pharmacogenomic Analyses

All pharmacogenomic measures will be listed, tabulated, and where appropriate, plotted. Correlation of response and pharmacogenomics measures will be explored. Results 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.

11.10. Patient-reported Outcomes and Medical Resource Utilization

FACT-Leu and EQ-5D-5L scores will be summarized at each time point. Medical resource utilization will be descriptively summarized by treatment group. Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit), frequencies of outpatient medical encounters and treatments will be calculated and tabulated.

11.11. 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 4.03. All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

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 subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

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 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 subject during the study will be provided as shift tables.

Electrocardiogram (ECG)

Electrocardiogram data will be presented by descriptive analysis only.

Vital Signs

Descriptive statistics of heart rate and supine blood pressure (systolic and diastolic) values and changes from baseline will be summarized. The percentage of subjects with clinically important changes from baseline will be summarized.

11.12. Independent Data Monitoring Committee

An IDMC, consisting of at least 2 clinicians and 1 statistician who are independent experts otherwise not participating in the study, will be established to review efficacy and safety results at the planned interim analyses. After the interim review, they will make recommendations regarding the continuation or stopping of the study. Study investigators and the sponsor's study team will not have access to the blinded data provided to the IDMC.

In addition, the IDMC will review safety data after the first 20 subjects have been followed for at least 1 month in Part B. The details will be provided in a separate IDMC charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, 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.

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 subject is the preferred method to inquire about adverse event occurrence. For some studies, subjects are not always able to provide valid verbal responses to open ended questions. In these circumstances, caregivers or guardians would provide information regarding adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local and systemic events for which the subject is specifically questioned.

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the subject is specifically not questioned.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. 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 Section 12.3.1, All Adverse Events, 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 subject 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 subject 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 drug 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 talacotuzumab and decitabine, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

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

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(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 drug. An alternative explanation, eg, concomitant drug(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 drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(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 drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI CTCAE Version 4.03. Any adverse event or serious adverse event not listed in the NCI CTCAE Version 4.03 will be graded according to investigator clinical judgment by using the standard grades as follows:

Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity.

Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

Grade 4: Life-threatening of disabling adverse event

Grade 5: Death related to the adverse event

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

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

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.

12.3. Procedures

Following Amendment 6, which incorporated the IDMC's recommendations to close enrollment to the study and discontinue talacotuzumab treatment for subjects receiving talacotuzumab + decitabine and offer to continue decitabine alone, all subjects will continue to be followed for survival and subsequent anti-cancer therapy. During the treatment phase with decitabine, subjects will be monitored for serious adverse events.

Following Amendment 7 and when 270 deaths have occurred or 6 months after the last subject is enrolled (whichever occurs first), follow up of subjects and data collection will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository.

12.3.1. 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 following the last dose of study drug. During the Follow-up Phase, adverse events of Grade 3 or higher that are considered related to study drug, as well as all related serious adverse events, should be followed until resolution.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, 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. Anticipated events will be recorded and reported as described in Attachment 4.

Treatment failure or relapse from CR/CRi should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms resulting from disease relapse/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1 Adverse Event Definitions and Classifications). Death should not be recorded as an adverse event or serious adverse event, but as the outcome of an adverse event. The adverse event that resulted in the death should be reported as a serious adverse event. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, 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.

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). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required).

For all studies with an outpatient phase, including open-label studies, the subject 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 subject 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 staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. 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).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject'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 drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject 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 cycle of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- 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.

Treatment failure or relapse from CR/CRi should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from treatment failure or relapse will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

12.3.3. Pregnancy

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. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment. 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 drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

12.4. 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 on the Contact Information page(s), which will be provided as a separate document.

13. 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 subjects, 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.

13.1. 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 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Talacotuzumab will be supplied as a lyophilized product containing 100 mg of active pharmaceutical ingredient (50 mg/mL after reconstitution with 2.0 mL sterile water for injection). It will be manufactured and provided under the responsibility of the sponsor. Decitabine will be supplied as a lyophilized powder in a single-dose vial of 50 mg per vial and provided by the sponsor. Decitabine powder should be reconstituted as outlined in the prescribing information.

14.2. Packaging

The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

Study drug will be supplied to the study sites. All talacotuzumab vials must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from exposure to light. Decitabine is supplied as a lyophilized preparation. Each 20 mL vial containing 50 mg decitabine should be stored at or below 25 °C.

Refer to the Site Investigational Product Manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes, and vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records on site.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

Following Amendment 7 and when 270 deaths have occurred or 6 months after the last subject is enrolled (whichever occurs first), follow up of subjects and data collection will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochures
- Pharmacy manual/study site investigational product manual
- Laboratory manual
- Patient-reported outcomes (PRO) questionnaires and user manuals
- Interactive web response system (IWRS) Manual
- Electronic data capture (eDC) Manual
- Sample ICF
- NCI CTCAE version 4.03

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is the first study of the combination of decitabine + talacotuzumab. These 2 agents are expected to have non-overlapping toxicity profiles; decitabine is primarily myelosuppressive while the most frequently reported toxicity from administration of talacotuzumab is infusion reactions. Additionally, the administration of the 2 agents is sequential and staggered which decreases the likelihood of toxicities due to direct interactions of the combination. Pharmacokinetic drug interactions are not anticipated because ADME properties of a nucleoside analog (decitabine) are different from those of a monoclonal antibody (talacotuzumab). The sponsor will evaluate the available safety of the combination of talacotuzumab and decitabine tested during Part A before proceeding to Part B.

Part B, the randomized portion of this study, will start after the RP2D for talacotuzumab is confirmed in Part A. Part B will use talacotuzumab at the RP2D + decitabine prior to the complete evaluation of safety for talacotuzumab + decitabine in Part A. The rationale for starting Part B is that randomization will provide a more informative safety analysis of the combination than that of the single-arm design of Part A. Furthermore, an IDMC will be formed to monitor safety and analyze efficacy. A comprehensive safety review of all available data from Part A and Part B will be conducted by the IDMC when approximately 10 subjects from each arm of Part B have been followed for 1 month. The sponsor, in collaboration with the IDMC, can amend the protocol, if needed, based on the results of those reviews. The IDMC will also analyze efficacy data, and if necessary, protect subjects from being exposed to an ineffective treatment.

After review of the data from Interim Analysis #2, the IDMC informed the Sponsor that the futility criterion for OS was met and that the CR rate did not meet per-protocol defined statistical significance. Given the lack of efficacy advantage of talacotuzumab + decitabine versus decitabine alone, the incidence of infusion-related reactions, and the complexities with premedications for drug administration, the benefit/ risk ratio is not favorable to continue treatment with talacotuzumab. The IDMC recommended closure of enrollment to the study and that subjects receiving talacotuzumab + decitabine should discontinue talacotuzumab treatment and may continue decitabine alone, according to Principal Investigator decision and subject agreement. All subjects will continue to be followed for survival and subsequent anti-cancer

therapy. During the treatment phase with decitabine, subjects will be monitored for serious adverse events.

Following Amendment 7 and when 270 deaths have occurred or 6 months after the last subject is enrolled (whichever occurs first), follow up of subjects and data collection will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository.

Infusion-related reactions have been reported with CSL362 in a Phase 1 study. Subjects in the current study will be monitored closely for safety. Premedication for prevention of infusion-related reactions will be mandatory prior to dosing for the first 4 cycles. If no infusion-related reactions, independent of severity, are seen for 2 consecutive cycles during the first 4 cycles of talacotuzumab treatment, then premedication may be modified per investigator discretion after discussion with the Sponsor for Cycle 5 and subsequent talacotuzumab treatments.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects 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 subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The volume of blood to be drawn is considered to be acceptable for subjects participating in a cancer clinical study and reasonable over the time frame of the study.[29]

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current 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 subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the Independent Ethics Committee/ Institutional Review Board (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 subjects)

- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects 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 subjects
- 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 subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject 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 subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure 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 drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects 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 subjects, 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).

16.2.3. Informed Consent

Each subject (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 subject 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 subjects 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. Subjects 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 subject will receive for the treatment of his or her disease. Subjects 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 subject 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 subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject 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 subject'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 subject.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

If the subject 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 subject or legally acceptable representative is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects 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 subjects confidential.

The informed consent obtained from the subject (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 subject 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 DNA, pharmacodynamics, biomarker, pharmacokinetics, and immunogenicity research is not conducted under standards appropriate for the return of data to subjects. 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 subjects 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.

16.2.5. 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 the function of talacotuzumab and decitabine, to understand the biology of AML, to understand differential drug responders, and to develop tests/assays related to talacotuzumab and decitabine. 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. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.4, Withdrawal From the Study (Withdrawal From the Use of Samples in Future Research).

16.2.6. 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 16, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. 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 subjects, 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) involves only logistic or administrative aspects of the study, the IRB (and IEC 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 (see Contact Information page(s) provided separately). 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.

17.2. Regulatory Documentation

17.2.1. 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.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug 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, subject 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 subject:

- 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

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

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: subject 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; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. In addition, 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).

Subject- and investigator-completed scales and assessments designated by the sponsor (eg, PRO assessments) will be recorded and will be considered source data.

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, 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 subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source 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 the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All CRF 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 CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, 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 CRF. Any such worksheets will become part of the subject's source documentation. Data must be entered into CRFs in English. The CRF must be completed as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective 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 a CRF are needed after the initial entry into the CRF, 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.

17.6. 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, 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.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, 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.

17.8. Monitoring

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 eCRFs 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 documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRF and source documents 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 documentation 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.

17.9. Study Completion/Termination

17.9.1. Study Completion/ End of Study

The end of study data collection is defined as when 270 deaths have occurred or 6 months after the last subject is enrolled, whichever occurs first. At that time, follow up of subjects will end. Subjects who are continuing to derive benefit from decitabine treatment as assessed by their investigator may continue to receive decitabine; during this period, only serious adverse events will be monitored and entered into the Company safety repository as described under Amendment 7.

17.9.2. 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 subjects by the investigator

- Discontinuation of further study drug development

17.10. 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. Subject 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.

17.11. Use of Information and Publication

All information, including but not limited to information regarding talacotuzumab and decitabine 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 pharmacogenomic or exploratory 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 talacotuzumab and decitabine, 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. Results of pharmacogenomics or exploratory 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 subject 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 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 substudy 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 12 months of the availability of the final data (tables, listings, graphs), 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 Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Sample 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

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

	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

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

	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

Attachment 2: Sample EQ-5D-5L

(English version for the UK)

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

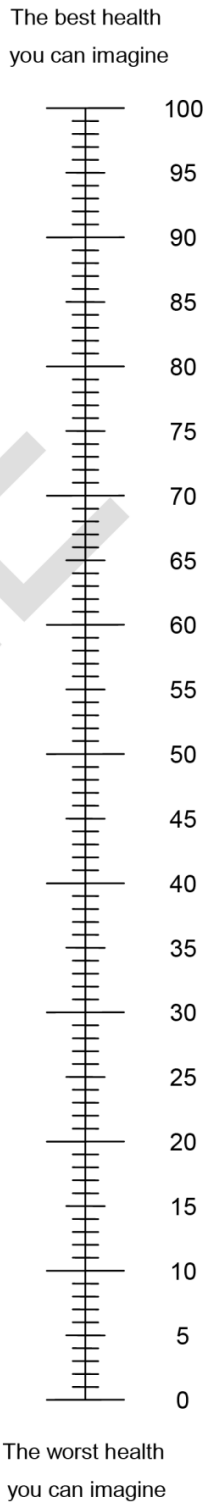
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 = ☐



Attachment 3: ECOG Performance Status Score

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
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, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Attachment 4: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

Disease Based:

- Thrombocytopenia
- Anemia
- Febrile neutropenia
- Leukopenia
- Pneumonia
- Sepsis
- Urinary tract infection
- Broncopneumonias
- Bacteremia
- Pyrexia
- Asthenia
- Fatigue
- Dyspnea
- Cardia dysrhythmias (i.e., atrial fibrillation)

Population Based:

- Congestive heart failure

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

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: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Aleksandra Rizo MD

Institution: Janssen Research and Development

Signature: [redacted] Date: 31 Oct 2017

(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.