Janssen Research & Development *

Clinical Protocol

A Phase 2 Proof-of-Concept Study to Separately Evaluate the Activity of Talacotuzumab (JNJ-56022473) or Daratumumab in Transfusion-Dependent Subjects with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) who are Relapsed or Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment

Protocol 56022473MDS2002; Phase 2
AMENDMENT 4

JNJ-56022473 (talacotuzumab)
JNJ-54767414 (daratumumab)

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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, LLC
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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	14 September 2016
Amendment 1	6 October 2016
Amendment 2	29 March 2017
Amendment 3	25 April 2017
Amendment 4	13 December 2018

Amendments are listed beginning with the most recent amendment.

Amendment 4 (13 December 2018)

The overall reason for the amendment To further clarify completion/end of study as the end of study data collection with continuation of daratumumab treatment according to the protocol for subjects continuing to derive benefit and to clarify that the monitoring of these subjects who continue to receive daratumumab according to the protocol will be for serious adverse events only.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify the 'end of study' as the end of study data collection and to clarify that the monitoring of subjects who continue to receive daratumumab according to the protocol will be for serious adverse events only.	
Synopsis: Overview of Study Design; Section 3.1 Overview of Study Design; Section 9.1.5 Clinical Cutoff and End of Study; 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 subjects who are deriving benefit will continue to receive daratumumab according to the protocol after study data collection ends. During this period after study data collection has ended, only serious adverse events will be monitored and only entered into the company safety repository.
Rationale: To clarify that the monitoring of subjects who continue to receive daratumumab according to the protocol will be for serious adverse events only.	
Synopsis: Evaluations; Section 6.1 Dosing Schedule; Section 8.2 Concomitant Medications; Section 9 Study Evaluations; Section 9.5 Safety Evaluations; Section 12.3.1 All Adverse Events; Section 16.1 Study-Specific Design Considerations	Clarified that for subjects who are continuing to receive daratumumab according to the protocol and derive benefit from treatment, only serious adverse events will be monitored and only entered into the company safety repository.
Time And Events Schedule – Daratumumab – Table Following Amendment 4	Added the Time and Events Schedule (Time And Events Schedule – Daratumumab – Table Following Amendment 4) with a note clarifying that for subjects who continue to receive daratumumab according to the protocol and derive benefit from the treatment after study data collection ends, only serious adverse events will be monitored and only entered into the company safety repository as of Amendment 4.

Applicable Section(s)	Description of Change(s)
Section 7 Treatment Compliance	Added a statement that electronic case report forms (eCRFs) will be closed after study data collection ends.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 3 (25 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 closes enrollment to the talacotuzumab arm as a precautionary measure due to benefit / risk considerations in patients with low-risk MDS and based on the occurrence of a Grade 4 infusion-related reaction in the first subject to receive talacotuzumab.

Applicable Section(s)	Description of Change(s)
Rationale: To close enrollment in the talacotuzumab arm following a Grade 4 infusion-related reaction that occurred in the first subject to receive talacotuzumab.	
Synopsis: Overview of Study Design; Section 3.1 Overview of Study Design; Section 3.2 Study Design Rationale; Section 5.1 Treatment Allocation; Section 16.1 Study-Specific Design Considerations	Added language to close enrollment to the talacotuzumab arm based on the occurrence of a Grade 4 infusion-related reaction in the first subject to receive talacotuzumab.

Amendment 2 (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 6.2.1 Talacotuzumab: 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: Provide time window for talacotuzumab dosing	

Applicable Section(s)	Description of Change(s)
Time and Events Schedule – Talacotuzumab; Section 6.1 Dosing Schedule	Provided details for the talacotuzumab dosing schedule and a time window of +/- 24 hours for talacotuzumab dosing
Rationale: Added premedication section to talacotuzumab Time and Events Schedule	
Time and Events Schedule – Talacotuzumab	Added preinfusion medication to Time and Events Schedule for talacotuzumab
Rationale: Clarified daratumumab dosing	
Time and Events Schedule – Daratumumab; Section 6.3.1 Dosing Schedule	Clarified daratumumab dosing schedule; Provided a time window of +/- 24 hours for daratumumab dosing
Rationale: Clarified daratumumab pre- and post-infusion medications	
Time and Events Schedule – Daratumumab Study Drug Administration	Added pre and postinfusion medication
Rationale: Added requirement for blood type assessment and indirect antiglobulin results	
Time and Events Schedule – Daratumumab Study Drug Administration	Added requirement for blood type assessment and indirect antiglobulin results on Day 1 of Cycle 1 only
Rationale: Clarified daratumumab dosing	
Section 6.3.2 Preparation and Administration of Daratumumab	Clarified daratumumab dosing and premedications
Rationale: Clarified daratumumab premedication of methylprednisolone	
Section 6.3.3 Daratumumab Premedications	Expanded footnote “a” to Table 4 to allow the reduction of corticosteroid (IV methylprednisolone 60mg or equivalent in Cycle 2 + subsequent cycles)
Rationale: update inclusion criterion number	
Section 4.1 Inclusion Criteria	Updated the number of inclusion criterion 9 to 9.1
Rationale: Bone marrow assessments for disease evaluation are not done by a central laboratory	
Section 9.2.3 Bone Marrow Assessment	Title of section changed to Clinical Bone Marrow Assessment; removed language stipulating central laboratory assessment
Rationale: Added Section for recommendations for Herpes Zoster reactivation prophylaxis	
Section 9.5.2 Prophylaxis for Herpes Zoster Reactivation	Added recommendations for herpes zoster reactivation prophylaxis
Rationale: To clarify daratumumab storage conditions	
Section 14.4 Preparation, Handling, and Storage	Modified language regarding daratumumab storage

Amendment 1 (6 October 2016)

The overall reason for the amendment: To correct an error in the Time and Events table under the collection of vital signs during the infusion of daratumumab and to revise the bilirubin inclusion criterion.

Applicable Section(s)	Description of Change(s)
Rationale: Corrected the collection of vital signs collected during the study.	
Time and Events Table	Corrected the collection of vital signs in the daratumumab arm
Rationale: Expanded inclusion limit for total bilirubin due to disease characteristics of MDS.	
Section 4.1, criterion #9	The inclusion limit for total bilirubin was increased from ≤1.5 x ULN to ≤3.0 x ULN.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor changes were made for consistency

SYNOPSIS

A Phase 2 Proof-of-Concept Study to Separately Evaluate the Activity of Talacotuzumab (JNJ-56022473) or Daratumumab in Transfusion-Dependent Subjects with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) who are Relapsed or Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment

Talacotuzumab (JNJ-56022473) is a humanized monoclonal antibody (mAb) that specifically targets the human interleukin-3 receptor alpha chain (IL-3Rα or CD123), and inhibits the signaling through this receptor.

Daratumumab is a human immunoglobulin G1 kappa (IgG1κ) mAb that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein.

Preclinical and clinical data indicate that talacotuzumab and daratumumab may eliminate immunosuppressive cell types in the bone marrow microenvironment of patients with MDS. Elimination of MDSCs (by both compounds) and Tregs (daratumumab only) may alter the immunosuppressive microenvironment and allow normal hematopoietic progenitor cells to differentiate, and ultimately improve clinical outcomes. Elimination of $CD123^+$ MDS blasts by talacotuzumab may further alter disease progression.

The purpose of this study is to separately evaluate 2 agents with different mechanisms of action that may be effective in subjects with low-risker MDS. The design of this study will allow an unbiased assessment of which agent, if either, will provide benefit to this patient population and further evaluate in clinical development. The generally accepted primary endpoint of transfusion independence (TI) has a subjective component based on transfusion practices that can be different across institutions, and randomizing subjects for talacotuzumab or daratumumab treatment with standardized inclusion and exclusion criteria and evaluation procedures will allow a more objective assessment of these 2 different agents.

OBJECTIVES, ENDPOINTS, AND HYPOTHESISES

Primary Objective

The primary objective of the study is to evaluate the efficacy (transfusion independence) of talacotuzumab (JNJ-56022473) or daratumumab in transfusion-dependent subjects with low or intermediate-1 risk MDS whose disease has relapsed during treatment with or is refractory to ESAs.

Primary Endpoint

The primary endpoint of this study is 8-week red blood cell (RBC) TI, defined as absence of RBC transfusion during any consecutive 56 days (8 weeks) post randomization.

Hypothesis

The primary hypothesis of this study is that the treatment with talacotuzumab or daratumumab separately will produce a TI rate 30% or greater against a minimal acceptable value of 15%. The statistical evaluation of the hypothesis will use a Bayesian approach to assess the likelihood of whether a true TI rate ≤15% can be ruled out.

OVERVIEW OF STUDY DESIGN

This is a multicenter, randomized, Phase 2, open-label study to evaluate the safety and efficacy of single-agent talacotuzumab or single-agent daratumumab in subjects with low or intermediate-1 risk MDS who are transfusion-dependent and whose disease has relapsed during or is refractory to ESA treatment. Approximately 60 subjects (30 to receive talacotuzumab and 30 to receive daratumumab) will be enrolled in this study.

Randomization will be stratified based on transfusion burden (4 or >4 units) prior to randomization, and then assigned randomly on a 1:1 basis to receive either talacotuzumab or daratumumab. Enrollment to the talacotuzumab arm was closed (refer to Section 3.1 Overview of Study Design for details). Transfusion burden is defined as the maximum number of RBC units transfused over any 8 consecutive weeks during the 16 weeks prior to randomization. The study consists of: a Screening Phase of up to 28 days during which subject eligibility will be reviewed and approved by the sponsor prior to randomization, a Treatment Phase that will extend from the first dose on Cycle 1 Day 1 until study drug discontinuation, and a Posttreatment Follow-up Phase beginning once the subject discontinues talacotuzumab or daratumumab.

Talacotuzumab will be administered at 9 mg/kg intravenously (IV) every 2 weeks. Daratumumab will be administered at 16 mg/kg IV weekly on Weeks 1 to 8, every 2 weeks for Weeks 9 to 24, and every 4 weeks thereafter. Cycle length is a 28 days for both agents. Study drugs will continue to be administered until disease progression, lack of response, unacceptable toxicity, withdrawal of consent, or study end.

The clinical cutoff for the purpose of the primary endpoint analysis will be 6 months after randomization of the last subject. The end of the study data collection is defined as either 1 year after the last subject has been randomized or anytime the sponsor terminates the study. At that time, study follow-up of subjects and study data collection will end. Subjects who are continuing to derive benefit from daratumumab treatment as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data collection has ended, only serious adverse events will be monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedule.

EVALUATIONS

Efficacy evaluations will include transfusion data, blood count assessments, and bone marrow biopsy and aspirate for disease assessment.

For all subjects in the talacotuzumab or daratumumab treatment groups, PK samples will be evaluated to determine serum concentration of talacotuzumab or daratumumab.

Serum concentrations of talacotuzumab or daratumumab and detection and characterization of anti-talacotuzumab or anti-daratumumab antibodies will be performed.

Biomarker evaluations will include immunophenotyping of immune cell populations, enumeration of CD123 and CD38 expression on suppressor cells, reduction of blasts, mutation analysis, and proteomic analysis.Safety will be assessed by adverse events, physical examinations, clinical laboratory parameters, electrocardiograms, vital sign measurements, ECOG performance status, and concomitant medication usage. A sponsor safety review committee will review all the safety data on a quarterly basis, or ad hoc, as needed.

The follow-up of subjects in the study and study data collection will end either 1 year after the last subject is randomized or anytime the sponsor terminates the study. Subjects who are continuing to derive benefit from daratumumab treatment as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data collection has ended, only serious adverse events will be monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedule.

STATISTICAL METHODS

There will be no formal statistical comparison between the 2 arms. Each treatment regimen will be analyzed separately to determine the likelihood that the true TI rate is 30% or greater against a minimum acceptable value of 15%. The planned sample size is approximately 30 subjects per treatment arm, which ensures at least 90% probability that the true TI rate is ≥15% if at least 8 subjects reach TI.

TIME AND EVENTS SCHEDULE - TALACOTUZUMAB

PHASE		Screening Phase	Treatment Phase (4-week cycles +/-3 days)				Posttreatment Follow-up Phase
Study Procedures	**Notes**	**Up to 28 days before first dose**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 until EOT Day 1, 15**	**EOT Visit Within 30 days after last dose**	**Survival Follow-up Every 16 weeks (+/- 7 days)**
Screening/Administrative							
Informed consent	Subjects must sign before any study-specific procedures are performed.	X					
Inclusion/exclusion criteria		X					
Medical history, blood typing, and demographics		X					
Study Drug Administration							
Dispense/administer study drug (+/- 24 hours)	Screening weight is baseline for dose calculation. Recalculate if weight changes >10% from screening.		X	X	X		
Preinfusion medications	All subjects receiving talacotuzumab must receive premedication during the first 4 cycles, as outlined in Section 6.2.2. If no infusion-related reactions are seen during the first 4 cycles of talacotuzumab treatment, then premedication is optional for subsequent talacotuzumab treatments. If an infusion-related reaction of any severity occurs in subsequent talacotuzumab treatments, premedication must be reintroduced.		X	X	X		
Safety Assessments							
Physical exam (including weight)	At post-screening visits, only a limited symptom-directed physical examination.	X	X[a]		Only Day 1[a]	X	
Vital signs	Vital signs should be measured and recorded (prior to study medication administration) and include heart rate and systolic/diastolic blood pressure, preferably while the subject is in a seated position.	X	X[a]		Only Day 1[a]	X	
12-lead ECG		X	X[a]				
Efficacy Assessments							
Transfusion history and status; myeloid growth factor treatment	Assessment of RBC transfusion requirements and myeloid growth factor use 16 weeks prior to randomization, at each 4-week cycle visit, disease evaluation visit,	X	X[a]		Only Day 1[a]	X	X (first visit and every 4-6 weeks if feasible)

PHASE		Screening Phase	Treatment Phase (4-week cycles +/-3 days)				Posttreatment Follow-up Phase
Study Procedures	**Notes**	**Up to 28 days before first dose**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 until EOT Day 1, 15**	**EOT Visit Within 30 days after last dose**	**Survival Follow-up Every 16 weeks (+/- 7 days)**
	and all unscheduled visits during treatment. Complete transfusion information must be collected, including both in-patient and out-patient transfusions.						

TIME AND EVENTS SCHEDULE – TALACOTUZUMAB

PHASE		Screening Phase	Treatment Phase (4-week cycles +/-3 days)				Posttreatment Follow-up Phase
Study Procedures	**Notes**	**Up to 28 days before first dose**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 until EOT Day 1, 15**	**EOT Visit Within 30 days after last dose**	**Survival Follow-up Every 16 weeks (+/- 7 days)**
Bone marrow aspirate/biopsy with cytogenetics	Bone marrow aspirate and biopsy with iron stain must be performed during screening or up to 12 weeks prior to first dose. Following the bone marrow at PR and CR, bone marrow should be repeated 4 to 8 weeks later for confirmatory purposes. The EOT bone marrow does not have to be performed if the prior assessment occurred within 8 weeks. Bone marrow assessments can be performed within a window of ± 7 days.	X	Every 24 weeks after C1D1, and at time of suspected PR, CR, or PD If PR/CR occurs, a bone marrow is collected every 24 weeks thereafter			X	
Response assessment	Per IWG 2006 (see Attachment 6)		Week 12, 24, 36, 48, 60, 72 and then every 24 weeks until PD			X	
ECOG performance status		X	X[a]		Only Day 1[a]	X	
Survival status							X
Biomarker Assessments							
Bone marrow biopsy	See Efficacy Assessments Section	X					
Bone marrow aspirate	See Efficacy Assessments Section	X	At time of suspected PR/CR and every 24 weeks thereafter until PD			X (or PD)	
Peripheral blood	Peripheral blood will be collected at specified visits and at the time of PR/CR and every 24 weeks thereafter. Immunophenotyping will be performed by flow cytometry and CyTOF.		X[a]	X[a]	Only Day 1 of Cycles 2, 4 and 6[a]	X (or PD)	

TIME AND EVENTS SCHEDULE – TALACOTUZUMAB

PHASE		Screening Phase	Treatment Phase (4-week cycles +/-3 days)				Posttreatment Follow-up Phase
Study Procedures	**Notes**	**Up to 28 days before first dose**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 until EOT Day 1, 15**	**EOT Visit Within 30 days after last dose**	**Survival Follow-up Every 16 weeks (+/- 7 days)**
Plasma	Plasma will also be collected at specified visits and at the time of PR/CR and every 24 weeks thereafter.		X[a]		Only Day 1 of Cycle 4[a]	X (or PD)	
Clinical Laboratory Assessments							
Hematology	Hematology laboratory assessments to determine subject eligibility must be performed within 14 days prior to first dose. For Cycle 1 Day 1, clinical laboratory assessments do not need to be repeated if the Screening tests were performed within 5 days of the first dose of study treatment.	X	X[a]	X[a]	X[a]	X	
Chemistry	Chemistry laboratory assessments to determine subject eligibility must be performed within 14 days prior to first dose. For Cycle 1 Day 1, clinical laboratory assessments do not need to be repeated if the Screening tests were performed within 5 days of the first dose of study treatment	X	X[a]		Only Day 1[a]	X	
Serum EPO level		X					
Serum ferritin, transferrin saturation		X					
Serology	HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody	X					
Serum β-hCG or urine pregnancy test	For women of childbearing potential only; must be performed within 14 days prior to first dose	X	Only if clinically indicated				
Ongoing Subject Review							
Concomitant therapy	Continuous from the time of signing ICF until 30 days after the end of dosing or until the start of subsequent anticancer treatment, if earlier	X	Continuous			X	
Adverse events	Continuous from the time of signing ICF until 30 days after the end of dosing or until the start of subsequent anticancer treatment, if earlier	X	Continuous			X	

TIME AND EVENTS SCHEDULE – TALACOTUZUMAB

PHASE		Screening Phase	Treatment Phase (4-week cycles +/-3 days)				Posttreatment Follow-up Phase
Study Procedures	**Notes**	**Up to 28 days before first dose**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 until EOT Day 1, 15**	**EOT Visit Within 30 days after last dose**	**Survival Follow-up Every 16 weeks (+/- 7 days)**
Subsequent therapy	Subsequent therapy to be collected throughout survival follow-up period					X	X

Abbreviations: C1D1=Cycle 1, Day 1; CR=complete remission; CyTOF=cytometry by time of flight; EOT=end-of-treatment; EPO=erythropoietin; PD=disease progression; PR=partial remission

a. To be performed before the start of the infusion.

TIME AND EVENTS SCHEDULE - TALACOTUZUMAB PHARMACOKINETICS AND IMMUNOGENICITY ASSESSMENTS

Visit/Timepoint			Talacotuzumab	
			PK Sample[a,b]	ADA (taken from PK sample)[a,c,d]
Cycle 1	Day 1	predose	X	X
		end of infusion	X	
Cycle 1	Day 15	predose	X	X
Cycle 2	Day 1	predose	X	X
Cycle 3	Day 1	predose	X	X
Cycle 4	Day 1	predose	X	X
		end of infusion	X	
Cycle 4	Day 15	predose	X	
Cycle 5	Day 1	predose	X	X
Cycle 6	Day 1	predose	X (Cycle 6 or Cycle 7)	X (Cycle 6 or Cycle 7)
Cycle 7	Day 1	predose		
EOT			X	X
Follow-up	4 and 8 weeks after last dose of talacotuzumab		X	X

ADA=anti-drug antibody, EOT=end-of-treatment, PK=pharmacokinetics

a. Sent to central laboratory.
b. Sample to be taken before the start of the infusion (-2 hours) and end of infusion sample to be taken 0.5 to 2 hours after the end of the infusion. Venous blood samples (5 mL per sample) will be collected for PK/ADA analysis and the serum will be divided into 3 aliquots (1 aliquot for PK analysis, 1 aliquot for antibodies to talacotuzumab analysis [when appropriate], and 1 aliquot as a backup).
c. An aliquot from the PK sample will be used to assess immunogenicity. A separate blood draw is not needed.
d. Sample to be taken at time of infusion-related reaction.

TIME AND EVENTS SCHEDULE – DARATUMUMAB

PHASE		Screening Phase	Treatment Phase (4-week cycles +/-3 days)						Posttreatment Follow-up Phase
Study Procedures	Notes	Up to 28 days before first dose	Cycle 1 Day 1	Cycle 1 Day 8, 15, 22	Cycle 2 Day 1, 8, 15, 22	Cycle 3, 4, 5, 6 Day 1, 15	Cycle 7 until EOT Day 1	EOT Visit Within 30 days after last dose	Survival Follow-up Every 16 weeks (+/- 7 days)
Screening/Administrative									
Informed consent	Subjects must sign before any study-specific procedures are performed.	X							
Inclusion/exclusion criteria		X							
Medical history, blood		X							

PHASE		Screening Phase	Treatment Phase (4-week cycles +/-3 days)						Posttreatment Follow-up Phase
Study Procedures	**Notes**	**Up to 28 days before first dose**	**Cycle 1 Day 1**	**Cycle 1 Day 8, 15, 22**	**Cycle 2 Day 1, 8, 15, 22**	**Cycle 3, 4, 5, 6 Day 1, 15**	**Cycle 7 until EOT Day 1**	**EOT Visit Within 30 days after last dose**	**Survival Follow-up Every 16 weeks (+/- 7 days)**
typing, and demographics									
Study Drug Administration									
Dispense/administer study drug (+/- 24 hours)	Screening weight is baseline for dose calculation. Recalculate if weight changes >10% from screening.		X	X	X	X	X		
Pre and postinfusion medications	Subjects will receive preinfusion medications before all daratumumab infusions, and postinfusion medications on the 2 days following all daratumumab infusions (beginning the day after the infusion). Refer to Sections 6.3.3 and 6.3.3.1 for additional information.		X	X	X	X	X		
Safety Assessments									
Physical exam (including weight)	At post-screening visits, only a limited symptom-directed physical examination.	X	X[a]		Only Day 1[a]	Only Day 1[a]	X[a]	X	
Vital signs	Vital signs should be measured and recorded (prior to study medication administration) and include heart rate and systolic/diastolic blood pressure, preferably while the subject is in a seated position.	X	X[a]		Only Day 1[a]	Only Day 1[a]	X[a]	X	
12-lead ECG		X	X[a]						
Efficacy Assessments									
Transfusion history and status; myeloid growth factor treatment	Assessment of RBC transfusion requirements and myeloid growth factor use 16 weeks prior to randomization, at each 4-week cycle visit, disease evaluation visit, and all unscheduled visits during treatment. Complete transfusion information must be collected, including both in-patient and out-patient transfusions	X	X[a]		Only Day 1[a]	Only Day 1[a]	Only Day 1[a]	X	X (first visit and every 4-6 weeks if feasible)

TIME AND EVENTS SCHEDULE - DARATUMUMAB

PHASE		**Screening Phase**	**Treatment Phase (4-week cycles +/-3 days)**						**Posttreatment Follow-up Phase**
Study Procedures	**Notes**	**Up to 28 days before first dose**	**Cycle 1 Day 1**	**Cycle 1 Day 8, 15, 22**	**Cycle 2 Day 1, 8, 15, 22**	**Cycle 3, 4, 5, 6 Day 1, 15**	**Cycle 7 until EOT Day 1**	**EOT Visit Within 30 days after last dose**	**Survival Follow-up Every 16 weeks (+/- 7 days)**
Bone marrow aspirate with cytogenetics and bone marrow biopsy	Bone marrow aspirate and biopsy with iron stain must be performed during screening or up to 12 weeks prior to first dose. Following the bone marrow at PR and CR, bone marrow should be repeated 4 to 8 weeks later for confirmatory purposes. The EOT bone marrow does not have to be performed if the prior assessment occurred within 8 weeks. Bone marrow assessments can be performed within a window of ± 7 days.	X	Every 24 weeks, at time of PR, CR, and at PD If PR/CR occurs, a bone marrow is collected every 24 weeks thereafter					X	
Response assessment	Per IWG 2006		Week 12, 24, 36, 48, 60, 72 and then every 24 weeks until PD					X	
ECOG performance status		X	X[a]		Only Day 1[a]	Only Day 1[a]	X[a]	X	
Survival status									X
Biomarker Assessments									
Bone marrow biopsy	See Efficacy Assessments Section	X							
Bone marrow aspirate	See Efficacy Assessments Section	X	At time of suspected PR/CR and every 24 weeks thereafter until PD					X (or PD)	
Peripheral blood	Peripheral blood will be collected at specified visits and at the time of PR/CR and every 24 weeks thereafter. Immunophenotyping will be performed by flow cytometry and CyTOF.		X[a]	Only Day 15[a]	Only Day 1[a]	Only Day 1 of Cycles 4 and 6[a]		X (or PD)	
Plasma	Plasma will also be collected at specified visits and at the time of PR/CR and every 24 weeks thereafter.		X[a]			Only Day 1 of Cycle 4[a]		X (or PD)	

TIME AND EVENTS SCHEDULE - DARATUMUMAB

PHASE		Screening Phase	Treatment Phase (4-week cycles +/-3 days)						Posttreatment Follow-up Phase
Study Procedures	**Notes**	**Up to 28 days before first dose**	**Cycle 1 Day 1**	**Cycle 1 Day 8, 15, 22**	**Cycle 2 Day 1, 8, 15, 22**	**Cycle 3, 4, 5, 6 Day 1, 15**	**Cycle 7 until EOT Day 1**	**EOT Visit Within 30 days after last dose**	**Survival Follow-up Every 16 weeks (+/- 7 days)**
Clinical Laboratory Assessments									
Hematology	Hematology laboratory assessments to determine subject eligibility must be performed within 14 days prior to first dose. For Cycle 1 Day 1, clinical laboratory assessments do not need to be repeated if the Screening tests were performed within 5 days of the first dose of study treatment.	X	X[a]	X	Only Day 1[a]	Only Day 1[a]	X	X	
Chemistry	Chemistry laboratory assessments to determine subject eligibility must be performed within 14 days prior to first dose. For Cycle 1 Day 1, clinical laboratory assessments do not need to be repeated if the Screening tests were performed within 5 days of the first dose of study treatment.	X	X[a]		Only Day 1[a]	Only Day 1[a]	X[a]	X	
Blood type assessment and indirect antiglobulin results	Prior to dosing on Day 1 of Cycle 1 only								
Serum EPO level		X							
Serum ferritin, transferrin saturation		X							
Serology	HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody	X							
Serum β-hCG or urine pregnancy test	For women of childbearing potential only; must be performed within 14 days prior to first dose	X	Only if clinically indicated						
Ongoing Subject Review									
Concomitant therapy	Continuous from the time of signing ICF until 30 days after the end of dosing or until the start of subsequent anticancer treatment, if earlier	X	Continuous					X	

TIME AND EVENTS SCHEDULE - DARATUMUMAB

PHASE		**Screening Phase**	**Treatment Phase (4-week cycles +/-3 days)**						**Posttreatment Follow-up Phase**
Study Procedures	**Notes**	**Up to 28 days before first dose**	**Cycle 1 Day 1**	**Cycle 1 Day 8, 15, 22**	**Cycle 2 Day 1, 8, 15, 22**	**Cycle 3, 4, 5, 6 Day 1, 15**	**Cycle 7 until EOT Day 1**	**EOT Visit Within 30 days after last dose**	**Survival Follow-up Every 16 weeks (+/- 7 days)**
Adverse events	Continuous from the time of signing ICF until 30 days after the end of dosing or until the start of subsequent anticancer treatment, if earlier	X	Continuous					X	
Subsequent therapy	Subsequent therapy to be collected throughout survival follow-up period							X	X

Abbreviations: C1D1=Cycle 1, Day 1; CR=complete remission; CyTOF=cytometry by time of flight; EOT=end-of-treatment; EPO=erythropoietin; PD=disease progression; PR=partial remission

a. To be performed before the start of the infusion.

TIME AND EVENTS SCHEDULE - DARATUMUMAB PHARMACOKINETICS AND IMMUNOGENICITY ASSESSMENTS

Visit/Timepoint			Daratumumab	
			PK Sample[a,b]	ADA (taken from PK sample)[a,c]
Cycle 1	Day 1	predose	X	X
		end of infusion	X	
Cycle 2	Day 1	predose	X	X
		end of infusion	X	
Cycle 3	Day 1	predose	X	X
		end of infusion	X	
Cycle 7	Day 1	predose	X	X
		end of infusion	X	
Cycle 12	Day 1	predose	X	X
		end of infusion	X	
Follow-up	4 and 8 weeks after last dose of daratumumab		X	X

ADA=anti-drug antibody, EOT=end-of-treatment, PK=pharmacokinetics
a. Sent to central laboratory.
b. Predose sample to be taken before the start of the infusion (-2 hours) and end of infusion sample to be taken within 2 hours after the end of the infusion. Venous blood samples (5 mL per sample) will be collected for PK/ADA analysis and the serum will be divided into 3 aliquots (1 aliquot for PK analysis, 1 aliquot for antibodies to daratumumab analysis [when appropriate], and 1 aliquot as a backup).
c. An aliquot from the PK sample will be used to assess immunogenicity. A separate blood draw is not needed.

TIME AND EVENTS SCHEDULE – DARATUMUMAB - TABLE FOLLOWING AMENDMENT 4

PHASE	
NOTE: After the end of study data collection, subjects who are deriving benefit may continue receiving daratumumab treatment, and will be monitored for serious adverse events that occur during treatment through resolution and entered only into the company safety repository as described under Amendment 4. These subjects will continue to be followed by the study physician according to local standard of care practices and in accordance with daratumumab dosing guidelines.	

ABBREVIATIONS

ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ALT	alanine aminotransferase
ARC	Anticipated Event Review Committee
AST	aspartate aminotransferase
ALP	alkaline phosphatase
Breg	regulatory B cell
C_{max}	maximum observed serum concentration
C_{min}	minimum observed serum concentration
CMML	chronic myelomonocytic leukemia
COPD	chronic obstructive pulmonary disease
CR	complete response
CyTOF	cytometry by time of flight
eCRF	electronic case report form
eDC	electronic data capture
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOT	end-of-treatment
EPO	erythropoietin
ESA	Erythropoiesis-Stimulating Agent
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
HI	hematologic improvement
HI-E	hematologic improvement-erythroid
HI-P	hematologic improvement-platelet
HI-N	hematologic improvement-neutrophil
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG1κ	immunoglobulin G1 kappa
IHC	immunohistochemistry
IMiD	immunomodulatory drug
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IRR	infusion-related reactions
IV	intravenous
IWRS	interactive web response system
IWG	International Working Group
mAb	monoclonal antibody
MDS	Myelodysplastic Syndrome
MDSCs	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
OS	overall survival
pDCs	plasmacytoid dendritic cells
PD	disease progression / progressive disease
PD	pharmacodynamics
PK	pharmacokinetic
PQC	poor quality complaint

PR	partial response
pRBC	packed red blood cell
RBC	red blood cell
SC	subcutaneous
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reactions
TI	transfusion independence
Treg	regulatory T cell
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WPSS	WHO classification-based Prognostic Scoring System

1. INTRODUCTION

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.

Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) are a heterogeneous group of malignant hematopoietic stem cell disorders that are characterized by cytopenias, myeloid dysplasia and a risk of transformation to acute myeloid leukemia.[3] In MDS, an increase of inflammatory cells is observed in the bone marrow microenvironment, which may lead to suppression of normal differentiation of hematopoietic cells via recruitment of various immunosuppressor cell types. The immunosuppressive environment is also thought to induce tolerance of MDS blasts and allows further accumulation of genetic aberrations leading to disease progression.

The primary immunosuppressive cell types found in MDS are myeloid-derived suppressor cells (MDSCs), which are a key component in suppressing normal immune cell function. Upon stimulation, they cause a reduction in T-cell proliferation and IFNγ secretion[2] and can inhibit NK cell function as well.[11] When analyzing the secretome of MDSCs, high levels of suppressive cytokines IL-10 and TGF-β were expressed in vitro.[2] Specifically in MDS, it has been shown by several groups that the frequency of MDSCs is increased in both the bone marrow and peripheral blood of patients with MDS compared to healthy controls.[6] Interestingly, MDSCs were also shown to alter normal hematopoiesis through direct contact with hematopoietic stem and progenitor cells in vitro, which may contribute to anemia.[2] Targeting these cells may improve anemias and lead to transfusion independence (TI) in MDS patients.

The standard prognostic tool in MDS is the International Prognostic Scoring System (IPSS), which classifies patients into low, intermediate-1, intermediate-2, and high risk categories on the basis of the percentage of bone marrow blasts, the karyotype, and the number of cytopenias. The median survival rates for the low, intermediate-1, intermediate-2, and high risk categories are estimated at 5.7, 3.5, 1.2, and 0.4 years, respectively.[3,7] Other prognostic systems have also been described, namely the WHO classification-based Prognostic Scoring System (WPSS)[25] and IPSS-Revised (IPSS-R).[8] The IPSS is more frequently referenced in clinical trials. Patients with low and intermediate-1 risk MDS are also often referred to as having "lower risk" disease, whereas those with intermediate-2 and high risk MDS are referred to as patients with "higher risk" disease.

Treatment Options for MDS

For patients with IPSS low and intermediate-1 risk MDS, the initial approach to treatment typically involves supportive care measures, ie, red blood cell (RBC) transfusions or erythropoiesis-stimulating agents (ESAs) or other hematopoietic growth factors, aimed at alleviating cytopenias. Approximately 40% of the patients will achieve an International Working Group (IWG)-defined hematologic improvement to ESAs for a median duration of 2 years. The Nordic MDS group has developed a model that identifies patients more likely to respond to ESAs. Those with low or no transfusion requirements (<2 packed red blood cell [pRBC] units/month) and a low serum erythropoietin (EPO) level (<500 units/L) have a higher response

rate than those with high transfusion needs (≥2 units/month) and serum EPO level (≥500 units/L); 74% versus 7%, respectively.[10]

A marker of disease severity appears to be associated with early ESA failure (no response to ESA or relapse within 6 months). Patients whose disease fails ESA early compared to later failure have a higher rate of transformation to acute myeloid leukemia (AML) (5-year cumulative incidence of 22% versus 9%, respectively; p=0.02) with a much shorter median overall survival (OS) (37 months versus 54 months, respectively; p=0.02).[15] This median survival is considerably shorter than predicted at the time of diagnosis.

For a small subset of patients with lower risk MDS that carry the del(5q) chromosomal abnormality, lenalidomide is approved by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) based on the data that shows approximately 60% of subjects achieving durable (>24 weeks) RBC TI. The median duration of response was approximately 2 years.

For the larger subset of patients, comprising about 90% of all lower risk MDS that does not have the del(5q) chromosomal abnormality, there is currently no universally accepted therapeutic option. Phase 2 and Phase 3 studies with lenalidomide have been conducted. Rates and durability of TI were lower than those observed in the cohorts with the del(5q) abnormality. Approximately one-quarter of patients (27%) who received lenalidomide achieved RBC TI, with median duration of response ranging from 33 to 41 weeks.[20,21]

Hypomethylating agents, approved for patients with higher-risk MDS, have been evaluated for patients with lower risk MDS with multiple cytopenias after failure of other agents. In one study of decitabine given to 65 subjects with lower risk MDS, 23% achieved an overall improvement rate as assessed by modified IWG response of PR or better.[5] In another study of 25 subjects, 44% achieved a CR or hematologic improvement (HI, IWG response).[22] In this MDS patient population, a study with subcutaneous azacitidine resulted in a 23% response rate; and 17% of subjects who were RBC transfusion dependent at baseline became transfusion independent.[24] Despite their efficacy, the hypomethylating agents are generally reserved for patients with higher risk MDS because of their myelosuppressive toxicity.

Most patients with IPSS low and intermediate-1 risk MDS who have failed to respond to ESAs eventually require long-term RBC transfusions. Patients with low-risk MDS who are transfusion-dependent, have limited treatment options and generally have poorer outcomes. Findings from a recent systematic literature review and meta-analysis reported a reduction in mortality in patients who were transfusion independent compared to those who were transfusion dependent.[9] In addition, iron toxicity is an inevitable consequent of frequent red-blood-cell transfusions.[19] Although data are preliminary regarding the role of MDSCs in MDS, experimental treatments with proposed mechanisms to treat the underlying pathophysiology of MDS and decrease dependence on transfusions and their resulting complications may be of benefit of patients in this population with a high unmet need for effective therapies.

1.1. Study Drugs

Talacotuzumab (JNJ-56022473) is a humanized monoclonal antibody (mAb) that specifically targets the human interleukin-3 receptor alpha chain (IL-3Rα or CD123), and inhibits the signaling through this receptor. Talacotuzumab has been engineered to have increased affinity to human FcγRIIIa (CD16) expressed on NK cells and, as a consequence, has an enhanced ability to induce NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) against target cells expressing CD123. In lower risk MDS, these cell types are primarily MDSCs and may include blasts. To date, one Phase 1 study (Study CSLCT-AML-11-73) has been completed for patients with AML in CR at high risk for relapse. This study established the dose and showed promising efficacy in small subset of patients with the primary mechanism of action being targeting CD123 on AML blasts. In addition, an ongoing Phase 2/3 study (Study 56022473AML2002) is being conducted for patients older than 65 years with AML who are not candidates for intensive chemotherapy. In these studies, approximately 78 subjects have been treated with talacotuzumab as of 15 June 2016. Infusion-related reactions have been observed. These are generally mild to moderate, although Grade 3 events have been reported. Other potential risks include hypersensitivity (as part of an infusion-related reactions or alone), increased risk of infection, impaired response to live virus vaccinations, and immunogenicity to talacotuzumab.

Daratumumab (JNJ-54767414) is a human immunoglobulin G1 kappa (IgG1κ) mAb that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. Daratumumab was approved as monotherapy by the FDA and the EMA for the treatment of patients with relapsed and refractory multiple myeloma. Daratumumab is thought to mediate these responses, in part, through the elimination of $CD38^+$ immunosuppressive cells (MDSCs, regulatory T cells [Tregs] and regulatory B cells [Bregs]) that synergizes with direct elimination of the myeloma cells.[17] The identified risks associated with daratumumab include infusion-related reaction and interference with blood typing. Increased risk for infection is a potential risk, with upper respiratory tract infection (17%) the most frequent infection.

For the most comprehensive nonclinical and clinical information regarding talacotuzumab and daratumumab, refer to the latest version of the respective Investigator's Brochures and Addenda.[12,13]

1.2. Overall Rationale for the Study

CD123 has been shown to be expressed on Lin^- $HLA\text{-}DR^{low}$ $CD11b^+$ $CD33^+$ MDSCs. Preliminary data demonstrated an increase in frequency of MDSCs in MDS patient samples compared to healthy controls (sponsor data on file).[2] More importantly, the MDSCs in patients with MDS exhibit high levels of expression of CD123 (sponsor data on file). It is hypothesized that talacotuzumab will eliminate $CD123^+$ MDSCs in patients with MDS through NK cell-mediated cytotoxicity, and promote effective hematological differentiation.

CD123 has also been regarded as a marker of leukemic stem cells (LSC), and overexpression of CD123 on LSCs has been shown to correlate to blast proliferation and poor prognosis in AML.[23]

Myelodysplastic syndromes, as a pre-leukemia status, are clonal disorders with enhanced risk of evolution towards AML,[26] and it has been shown that $CD123^+$ LSCs were increased in patients with MDS compared to healthy controls.[27] Although the overall frequency of blasts in lower risk MDS is determined by having less than 5% blasts in the bone marrow, the $CD123^+$ LSCs in MDS patients display similar malignant features observed in $CD123^+$ LSCs in AML.[18] Therefore, talacotuzumab may also eliminate $CD123^+$ blasts in lower risk MDS patients and augment progression of disease.

Preliminary data on MDS patient samples has also shown high levels of expression of CD38 on MDSCs (sponsor data on file). In patients with multiple myeloma, MDSCs have been shown to express CD38, and are depleted after the first daratumumab infusion. More importantly, the MDSCs are sensitive and remain sensitive throughout daratumumab treatment.[17] Therefore, it is also hypothesized that daratumumab will target $CD38^+$ MDSCs in patients with MDS.

Lastly, Tregs have also been shown to be involved in the immunosuppressive microenvironment of low to intermediate 1-risk MDS patients.[16] Univariate analysis of overall and progression-free survival of 38 low to intermediate 1-risk MDS patients showed that patients with increased numbers of Tregs (above the median) had a lower progression-free and OS than patients with less than median number of Tregs.[14] In patients with multiple myeloma, CD38 has been shown to be expressed on a subset of Tregs, and the $CD38^+$ subset of Tregs has been shown to be highly immunosuppressive of T cell activity compared to $CD38^-$ Tregs. Importantly, this highly immunosuppressive fraction of Tregs is targetable by daratumumab[17] and therefore may also be a therapeutic target in patients with low-risk MDS. Reducing highly immunosuppressive $CD38^+$ Tregs may alter the progression of disease.

These data indicate that talacotuzumab and daratumumab may eliminate immunosuppressive cell types in the bone marrow microenvironment of patients with MDS. Elimination of MDSCs (both compounds) and Tregs (daratumumab only) may alter the immunosuppressive microenvironment and allow normal hematopoietic progenitor cells to differentiate, and ultimately improve clinical outcomes. Lastly, elimination of $CD123^+$ MDS blasts by talacotuzumab may further alter disease progression.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESISES

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objectives

The primary objective of the study is to evaluate the efficacy (transfusion independence) of talacotuzumab (JNJ-56022473) or daratumumab in transfusion-dependent subjects with low or intermediate-1 risk MDS whose disease has relapsed during treatment with or is refractory to ESAs.

Secondary Objectives

- To evaluate the safety of talacotuzumab or daratumumab in the study population
- To evaluate the clinical benefit of talacotuzumab and daratumumab in this study population through:
  - Time to TI and duration of TI
  - Rate of HI, CR, and PR
  - Overall survival (OS)
  - Progression to AML
  - Rate and amount of supportive care, including transfusions and myeloid growth factors
- To characterize the PK of talacotuzumab and daratumumab in the study population
- To evaluate the immunogenicity of talacotuzumab and daratumumab in subjects with MDS

Exploratory Objectives

The tertiary/exploratory objectives of this study are:

- To evaluate pharmacodynamic biomarkers for talacotuzumab activity
- To determine CD123 and CD38 expression and to explore the association with clinical outcomes

2.1.2. Endpoints

Primary Endpoint

The primary endpoint is 8-week RBC TI, defined as absence of RBC transfusion during any consecutive 56 days (8 weeks) post randomization.

Secondary Endpoints

The secondary endpoints of this study are:

- Transfusion independence lasting 168 days (24 weeks)
- Time to TI
- Duration of TI
- Transfusions and myeloid growth factors usage
- HI (including HI-E, HI-P, HI-N), CR, PR and cytogenetic response per IWG 2006
- Overall survival
- Progression to AML

Exploratory Endpoint

- Immunophenotyping of the bone marrow and peripheral blood by flow cytometry (MDSC, blasts, basophils, pDC, T and B cells, NK cells, and immunogenicity).

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

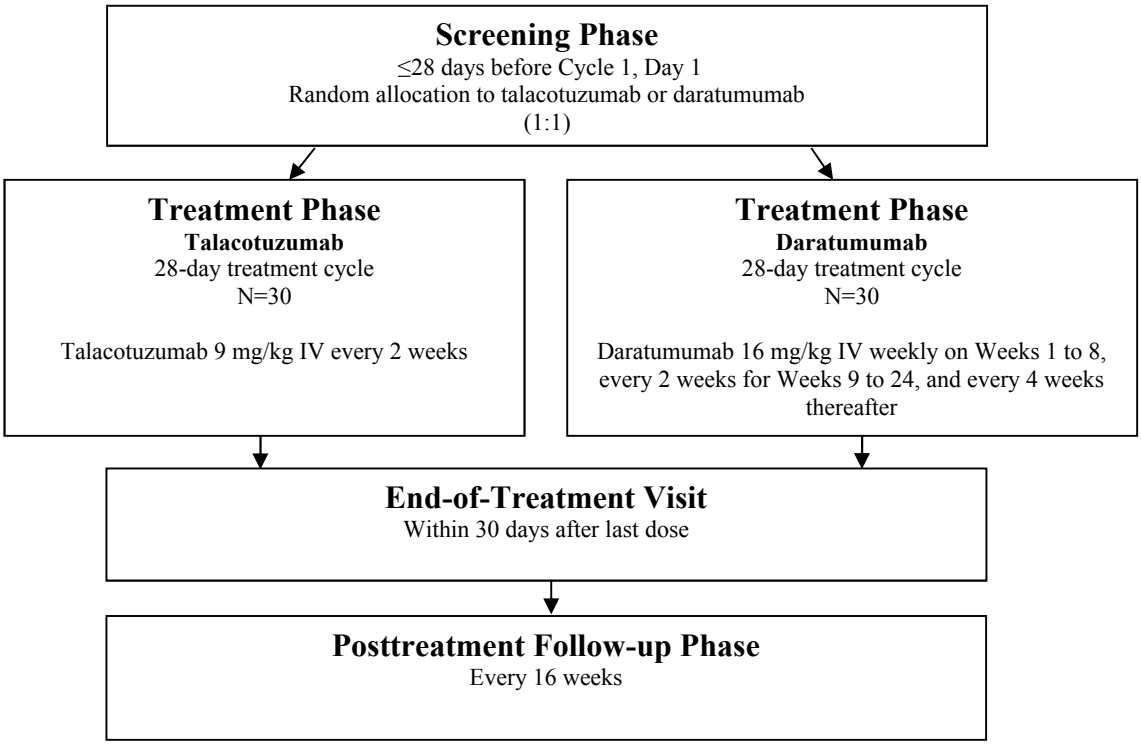
The primary hypothesis of this study is that the treatment with talacotuzumab or daratumumab separately will produce a TI rate 30% or greater against a minimal acceptable value of 15%. The statistical evaluation of the hypothesis will use a Bayesian approach to assess the likelihood of whether a true TI rate ≤15% can be ruled out.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter, randomized, Phase 2, open-label study to evaluate the safety and efficacy of single-agent talacotuzumab or single-agent daratumumab in subjects with low or intermediate-1 risk MDS who are transfusion-dependent and whose disease has relapsed during or is refractory to ESA treatment. Approximately 60 subjects (30 to receive talacotuzumab and 30 to receive daratumumab) will be enrolled in this study. There will be no statistical hypothesis testing, and each arm will be assessed separately without formal comparison between the 2 arms. Statistical methods focus on the evaluation of the likelihood that either treatment regimen will result in a true TI rate of 30% or greater against a minimum acceptable value of 15%. The planned sample size is approximately 30 subjects per treatment arm, which will ensure at least 90% probability that the true TI rate is greater than the minimum acceptable value 15% if at least 8 subjects reach TI. A diagram of the study design is provided below in Figure 1.

Figure 1: Schematic Overview of the Study



Note: As a precautionary measure, due to benefit / risk considerations for patients with low-risk MDS, enrollment to the talacotuzumab arm is closed based upon the occurrence of a Grade 4 infusion-related reaction in the first subject to receive talacotuzumab. The IWRS was modified to only permit enrollment to the daratumumab arm of the study.

The end of study data collection is defined as either 1 year after the last subject is randomized or anytime the sponsor terminates the study. At that time, study follow-up of subjects and study data collection will end. Subjects who are continuing to derive benefit from daratumumab treatment as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data collection has ended, only serious adverse events will be monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedule.

3.2. Study Design Rationale

Inflammatory changes are a prominent feature in MDS with increased populations of inflammatory cells in the bone marrow microenvironment. Inflammation in the bone marrow microenvironment leads to suppression of normal differentiation of hematopoietic cells via recruitment of suppressor cells. Myeloid-derived suppressor cells are thought to be a key component in suppressing normal immune cell function, and may have a profound role in the pathogenesis of MDS. The immunosuppressive environment is thought to promote tolerance to MDS blasts allowing accumulation of additional genetic aberrations. Targeting the inflammatory changes by eliminating either CD123- or CD38-expressing MDSCs may be a beneficial approach to the management of MDS.

Rationale for Randomization

Randomization will be used to allocate subjects to treatment groups. Although there is no formal statistical comparison between the 2 treatment groups, randomization can enhance the validity of statistical assessments to facilitate the decision making for further development of either or both treatment therapies if both treatment arms have met the primary objective. The primary endpoint of this study is defined by transfusion, and randomization can alleviate potential biases due to differences in transfusion practices across different sites and different countries. Enrollment to the talacotuzumab arm was closed (refer to Section 3.1 Overview of Study Design for details).

Rationale for Study Population

Limited treatment options are available for patients who are RBC-transfusion dependent and who have IPSS low risk or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment. An unmet need exists for agents that reduce the transfusion burden of these patients. The median survival for patients with low-risk MDS for whom ESA treatment has failed is about 3.5 years, which is considerably shorter than predicted at the time of diagnosis.[4,15] Furthermore, emerging data describe the role of MDSCs as well as Tregs in the pathogenesis of MDS. Targeting CD123 or CD38 on MDSCs with talacotuzumab or daratumumab, respectively, may show clinical benefit in patients with low-risk MDS.

Rationale for Endpoints

Transfusion independence for 8 weeks is a clinically meaningful and robust endpoint that is included in the IWG response criteria, and has been the basis for regulatory approvals.

The rate of HI-E will provide further explanation of the hematologic response (as per IWG criteria). Progression to AML and OS are important endpoints considering that the natural history of MDS progression includes transformation to AML in a proportion of patients.

The depth of the response will be captured by assessment of CR and PR. Duration of responses will be assessed. Subjects will be followed for OS.

3.3. Dose Rationales for Talacotuzumab and Daratumumab

Dose Rationale for Talacotuzumab

The proposed 9 mg/kg every 2 weeks (q2w) dose was selected based on analysis of the PK, CD123 receptor occupancy (RO), pharmacodynamic (PD), and safety data generated in the Phase 1 study for patients with AML in CR at high risk for relapse (CSLCT-AML-11-73).

The 9 mg/kg q2w dose level has been selected as the talacotuzumab recommended Phase 2 dose for patients with AML. It is the only dose level being tested in the ongoing Phase 2/3 study for talacotuzumab in patients older than 65 years with AML who are not candidates for intensive chemotherapy (Study 56022473AML2002).

Dose Rationale for Daratumumab

The dose and schedule used in this study (16 mg/kg weekly for 8 weeks, every 2 weeks for 16 weeks, and every 4 weeks thereafter) is the approved dosing regimen of daratumumab for the treatment of subjects with relapsed and refractory multiple myeloma. This dose was selected based on an acceptable safety profile, maximal clinical activity, and pharmacokinetics consistent with saturation of the target. This dose and similar schedules have been shown to be tolerable in several combination studies.

4. SUBJECT POPULATION

Subject eligibility will be reviewed and approved by the sponsor during the Screening Phase. Screening will be performed within 28 days prior to randomization.

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 subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

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

1. 18 years of age

2. MDS according to World Health Organization (WHO, Attachment 1) criteria confirmed by bone marrow aspirate and biopsy within 12 weeks prior to first dose. A local laboratory report from this diagnostic bone marrow aspirate and biopsy must be approved by the sponsor.

3. IPSS low risk or intermediate-1 risk MDS (Attachment 2)

4. RBC transfusion dependent

   - Received at least 4 units of RBCs over any 8 consecutive weeks during the 16 weeks prior to randomization
   - Pretransfusion Hb must have been ≤9.0 g/dL

   Source documentation for transfusions verified by the sponsor.

5. Relapsed/refractory to ESA treatment; the sponsor must verify this diagnosis as defined by meeting any of the criteria below:

   - Received at least 8 weeks of treatment with a minimum weekly dose of epoetin alfa 40,000 U, epoetin beta 30,000 U or darbepoetin alfa 150 mcg (or equivalent agent/dose) without having achieved a Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement by at least 4 units over 8 weeks
   - Transfusion dependence or reduction in Hb by ≥1.5 g/dL after hematologic improvement, in the absence of another explanation
   - Endogenous serum EPO level >500 mU/mL

   Source documentation for failure of ESA treatment verified by the sponsor

6. Adequate iron stores, defined as transferrin saturation greater than 20% and serum ferritin greater than 400 ng/mL, measured within the screening period, or adequate iron stores as demonstrated by recent (within 12 weeks prior to first dose) bone marrow examination with iron stain.

7. ECOG performance status 0, 1 or 2 (Attachment 3)

8. Hematology laboratory test values within the following limits:

   - ANC ≥1.0 x 10^9/L (ie, ≥1,000/mm^3) independent of growth factor support. For the screening ANC to be considered growth factor independent, a 7-day period after stopping the growth factor should be observed, or 7 half-lives of growth factor used, whichever is longer.
   - Platelets ≥50 x 10^9/L independent of platelet transfusion support. For the screening platelets to be considered independent of platelet transfusion support, platelet count must be stable for 3-4 days after the transfusion.

9. Criterion numbering modified per Amendment 2

9.1 Biochemical laboratory test values must be within the following limits:

   - Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤2.5 times the upper limit of normal (x ULN)
   - Creatinine clearance >40 mL/min

- Total bilirubin ≤3.0 x ULN, except for subjects with Gilbert syndrome

10. Women of childbearing potential and men who are sexually active must be practicing highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) during and after the study. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies. Men must agree to not father a child or donate sperm during and after the study. Women must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction. For females and males, these restrictions apply for at least 3 months after the last dose of study drug.

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

12. 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. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

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

1. Known allergies, hypersensitivity, or intolerance to talacotuzumab and daratumumab or their excipients (refer to Investigator's Brochure)
2. Received any chemotherapy, immunomodulatory or immunosuppressive therapy, corticosteroids (>30 mg/day prednisone or equivalent) within 28 days prior to randomization
3. Received other treatments for MDS within 28 days prior to first dose (eg, azacitidine, decitabine, lenalidomide, ESA (8 weeks for long-acting ESAs)
4. History of hematopoietic stem cell transplant
5. Del(5q) karyotype unless treatment with lenalidomide has failed. Failure is defined as either: 1) having received at least 3 months of lenalidomide treatment without RBC transfusion benefit (IWG 2006); 2) progression or relapse after hematologic improvement with lenalidomide (IWG 2006); 3) discontinuation of lenalidomide due to toxicity; or 4) unable to receive lenalidomide due to a contraindication. Source documentation for lenalidomide treatment failure must be verified by the sponsor.
6. Anemia attributed to factors other than MDS (including hemolysis, chronic renal failure, hepatitis, gastrointestinal bleeding)

7. Major surgery within 4 weeks prior to first dose (excludes the placement of a vascular access device and other minor surgical procedures)

8. Active malignancy other than MDS ≤3 years before first dose, except

   - Adequately treated non-melanoma skin cancer or lentigo maligna without current evidence of disease
   - Adequately treated cervical carcinoma in situ without current evidence of disease

9. Clinically significant cardiovascular disease including:

   - myocardial infarction within 6 months of screening
   - unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, cardiac disease meeting New York Heart Association Class 3-4 definition, Attachment 4)
   - uncontrolled or symptomatic cardiac arrhythmias
   - screening 12-lead ECG showing a baseline corrected QT interval (QTc) >470 msec

10. Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal

11. Known moderate or severe persistent asthma within the past 2 years (see Attachment 5), or uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.

12. Uncontrolled active systemic infection requiring IV antibiotics

13. Known history of human immunodeficiency virus (HIV) infection

14. Active systemic hepatitis infection requiring treatment or other clinically active liver disease

15. Females who are pregnant or are breastfeeding

16. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety, or put the study outcomes at undue risk. 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 that could prevent, limit, or confound the protocol-specified assessments

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. A woman of childbearing potential must remain on a highly effective method of birth control (see inclusion criteria) during the study. These restrictions apply for 3 months after the end of dosing.

2. A man who is sexually active with a woman of childbearing potential must use a highly effective adequate method of birth control and all men must also not donate sperm during the study. These restrictions apply for 3 months after the end of dosing.

3. Section 8 details prestudy and concomitant therapies used in this study.

5. TREATMENT ALLOCATION AND BLINDING

5.1. Treatment Allocation

Central randomization will be implemented in this study using an IWRS. Randomization will be stratified based on transfusion burden (4 or >4 units) prior to randomization, and then assigned randomly on a 1:1 basis to receive either talacotuzumab or daratumumab. Transfusion burden is defined as the maximum number of RBC units transfused over any 8 consecutive weeks during the 16 weeks prior to randomization. Enrollment to the talacotuzumab arm was closed (refer to Section 3.1 Overview of Study Design for details) and the IWRS was modified to only permit enrollment to the daratumumab arm of the study.

6. DOSAGE AND ADMINISTRATION

Talacotuzumab and daratumumab are the investigational medicinal products in this study and will be provided by the sponsor.

Subjects may receive treatment until disease progression, lack of response, unacceptable toxicity, withdrawal of consent, or study end. Continuation of treatment for subjects who are not deriving benefit, ie, after 6 months of treatment a subject has not achieved HI-E or RBC TI for ≥8 weeks, should be discussed with the sponsor.

Supportive Care

All subjects will receive supportive care (including transfusions if Hb ≤11 g/dL or myeloid growth factors) as needed per investigator discretion and according to local standard practices. Should an exceptional situation arise where it is deemed clinically necessary to give a transfusion for an Hb >11 g/dL, the sponsor should be notified.

6.1. Dosing Schedule

Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedule. Subjects should start study treatment within 72 hours after randomization. A

window of ±3 days is allowed for Day 1 of each cycle visits to the clinic. Each cycle is 28 days. The first visit of a cycle should be 4 weeks after the start of the previous cycle. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration

Study drug is to be administered as described in the Time and Events Schedules.

Talacotuzumab 9 mg/kg will be administered on Days 1 and 15 for all cycles. Daratumumab 16 mg/kg will be administered on Days 1, 8, 15, and 22 (+/- 24 hours) for Cycles 1 and 2; on Days 1 and 15 (+/- 24 hours) for Cycles 3 to 6; and on Day 1 (+/- 24 hours) for all subsequent cycles. Cycles may be delayed due to drug-related toxicities (See Sections 6.2.3 and 6.3.5).

The follow-up of subjects in the study and study data collection will end either 1 year after the last subject is randomized or anytime the sponsor terminates the study. Subjects who are continuing to derive benefit from daratumumab treatment as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data collection has ended, only serious adverse events will be monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedule.

6.2. Talacotuzumab

6.2.1. 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 180 minutes using an infusion pump. The talacotuzumab treatment will be administered per the dosing schedule described in Section 6.1. If an infusion-related reaction is observed during the administration of talacotuzumab, then follow the procedures described in Section 6.2.4. The sponsor may modify the infusion rates or the preinfusion medications prospectively based upon the information collected to date from this and other studies. Additional details for administration times and rates, as well as preinfusion medications, will be provided in the administration guidelines (study site investigational product and procedures manual).

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 Three Cycles: Initiate the IV infusion at a rate of 20 mL/hr. In the absence of any infusion-related reaction during the first 30 minutes, increase the infusion rate to 40 mL/hr for 30 minutes. If no infusion reaction is observed during this 30 minute period, increase the infusion rate by 40 mL/hr increments 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.

Subsequent Cycles (after the first 3 cycles): If no infusion reaction observed in the first 3 cycles, initiate the IV infusion at a rate of 40 mL/hr for 30 minutes. 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.

6.2.2. Talacotuzumab: Premedication

All subjects receiving talacotuzumab must receive premedication during the first 4 cycles, as outlined in Table 1. If no infusion-related reactions are seen during the first 4 cycles of talacotuzumab treatment, then premedication is optional for subsequent talacotuzumab treatments. If an infusion-related reaction of any severity occurs in subsequent talacotuzumab treatments, premedication must be reintroduced.

Table 1: Premedication for Subjects Receiving Talacotuzumab

Treatment Cycle	Infusion-related Reaction	Mandatory Premedication	Optional Premedication
Cycle 1 - Cycle 4		Methylprednisolone (100 mg IV)[a] 1-2 hours prior to infusion Dexamethasone (8 mg IV or PO) approx. 12 and 3 hours prior to infusion Leukotriene inhibitor (montelukast 10 mg PO, or equivalent) within 1-2 hours prior to infusion Acetaminophen (paracetamol) 650 – 1000 mg IV or PO approx.1 hour prior to infusion Antihistamine (diphenhydramine 25 – 50 mg IV or PO)[b] approx. 1 hour prior to infusion	Additional doses of corticosteroids prior to treatment with talacotuzumab may be given at the discretion of the investigator
Cycle 5 + Subsequent cycles	**If Prior Event:**	Methylprednisolone (100 mg IV)[a] 1-2 hours predose Dexamethasone (8 mg IV or PO) approx. 12 and 3 hours prior to infusion Leukotriene inhibitor (montelukast 10 mg PO, or equivalent) within 1-2 hours prior to infusion Acetaminophen (paracetamol) 650 – 1000 mg IV or PO approx.1 hour prior to infusion Antihistamine (diphenhydramine 25 – 50 mg IV or PO)[b] approx. 1 hour prior to infusion	Additional doses of corticosteroids prior to treatment with talacotuzumab may be given at the discretion of the investigator
	No Prior Event for 2 consecutive cycles:	Premedication may be modified per investigator discretion and after discussion with the sponsor	

a. 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.
b. Or similar sedating antihistamine per institutional standards; avoid the use of promethazine

6.2.3. Talacotuzumab Dosing Modifications

Refer to Section 6.2.4 for details on management of infusion-related reactions.

Dose delay is the primary method for managing talacotuzumab-related toxicities.

A dose delay should occur if any of the following criteria are met:

- 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 only be allowed to continue treatment if the investigator and sponsor believe it is in the best interest of the subject. However, this must be approved by the sponsor.

6.2.4. Management of Talacotuzumab Hypersensitivity/Infusion-related Reactions

Subjects should be carefully observed during infusions. It is recommended that subjects are monitored for at least 1 hour after the infusion has been completed.

Subjects who experience treatment-emergent adverse events during the IV infusion of talacotuzumab will be treated according to the investigator's judgment and best clinical practice. It is suggested that standing orders are readily available so that timely treatment can be provided to patients who experience infusion-related reactions. The following guidelines are suggestions for how reactions may be managed:

- 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 permanently discontinued and no additional talacotuzumab should be administered to the subject.

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

If an infusion-related reaction develops, then the infusion should be temporarily interrupted and the actions in Table 2 should be taken.

Table 2: Management of Talacotuzumab Infusion-related Reactions

Severity [per CTCAE 4.03]	Recommended action
Grade 1 or Grade 2	• If the investigator assesses a TEAE to be related to the talacotuzumab, pause infusion • When the subject's condition is stable, the infusion may be restarted at the investigator's discretion. The infusion rate should be at half the previous rate – Subsequently, the infusion rate may be increased at the investigator's discretion but should not exceed 150 mL/hr 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
Grade 3	• For infusion-related TEAEs that are Grade 3, stop infusion • Observe subject carefully until resolution of the TEAE or until the severity 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 150 mL/hr at any time. – If the severity 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.
Grade 4	• For infusion-related TEAEs that are Grade 4, stop infusion • Discontinue study drug

6.3. Daratumumab

6.3.1. Dosing Schedule

Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedules. Subjects should start study treatment within 72 hours after randomization. A window of ±3 days is allowed for Day 1 of each cycle visits to the clinic. Each cycle is 28 days. The first visit of a cycle should be 4 weeks after the start of the previous cycle. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. In Cycles 1 through 6, weekly or bi-weekly daratumumab infusions may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject.

6.3.2. Preparation and Administration of Daratumumab

The infusion solution will be prepared as a 1,000-mL (first dose) or 500-mL (second and subsequent doses) dilution of daratumumab in sterile, pyrogen-free 0.9% NaCl. Preparation of infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 μM) during the infusion. Manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to each pharmacy and site.

The daratumumab dose administered will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. The dose of daratumumab will remain constant throughout the study, unless the subject's weight changes more than 10% from Cycle 1 Day 1. All infusions will be planned as outpatient visits. The daratumumab treatment will be administered per the dosing schedule described in Section 6.1.

The dilution volumes, initial infusion rates, and increment of infusion rates for the first, second, and subsequent doses in the absence of an infusion-related reaction >Grade 1 are provided in Table 3. The first infusion, with a volume of 1,000 mL, takes approximately 8 hours; the second and subsequent infusions, with volumes of 500 mL, take approximately 4 hours. The maximum infusion rate for all infusions is 200 mL/hour. The sponsor may modify the infusion rates or the preinfusion medications prospectively based upon the information collected to date from this and other studies. Additional details for administration times and rates, as well as preinfusion medications, will be provided in the administration guidelines (study site investigational product and procedures manual).

Table 3: Daratumumab Infusion Rates

	Dilution Volume	Initial Infusion Rate (first hour)	Incremental Increases in Infusion Rate	Maximum Infusion Rate
First infusion	1,000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

a. Modified rates should only be used if the first infusion of daratumumab was well tolerated as defined by an absence of >Grade 1 infusion-related reactions during the first 3 hours.
b. Modified rates should only be used if the first 2 infusions of daratumumab were well tolerated as defined by an absence of >Grade 1 infusion-related reactions during a final infusion rate of ≥100 mL/hr.

As noted in the Time and Events Schedule, vital signs should be monitored extensively on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab. For all other infusions, vital signs should be measured before the start of the infusion and at the end of the infusion. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

6.3.3. Daratumumab: Premedication

All subjects receiving daratumumab must receive premedication as outlined in Table 4. On daratumumab infusion days, subjects will receive the following medications up to 3 hours before the dose of daratumumab.

Table 4: Premedication for Subjects Receiving Daratumumab

Treatment Cycle	Mandatory Premedication	Optional Premedication Strongly recommended by Sponsor
Cycle 1	Methylprednisolone (100 mg IV or PO) [a] within 3 hours prior to infusion Acetaminophen (paracetamol) 650 – 1000 mg IV or PO within 3 hours prior to infusion Antihistamine (diphenhydramine 25 – 50 mg IV or PO)[b] within 3 hours prior to infusion	Leukotriene inhibitor (montelukast 10 mg PO, or equivalent) within 3 hours prior to infusion Additional doses of steroids prior to treatment with daratumumab may be given at the discretion of the investigator.
Cycle 2 + Subsequent cycles	Methylprednisolone (60-100 mg IV or PO)[a] within 3 hours prior to infusion Acetaminophen (paracetamol) 650 – 1000 mg IV or PO within 3 hours prior to infusion Antihistamine (diphenhydramine 25 – 50 mg IV or PO)[b] within 3 hours prior to infusion	Leukotriene inhibitor (montelukast 10 mg PO, or equivalent) within 3 hours prior to infusion Additional doses of steroids prior to treatment with daratumumab may be given at the discretion of the investigator.

a. Substitutions for methylprednisolone are allowed, please refer to Attachment 7 for conversion table. Following the second infusion, the dose of methylprednisolone or equivalent can be reduced to 60 mg
b. Or similar sedating antihistamine per institutional standards; avoid the use of promethazine (see Attachment 8 for list of antihistamines that may be used)

If necessary, all PO preinfusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion.

6.3.3.1. Daratumumab: Postinfusion Medication

Postinfusion medication should be administered to reduce the risk of delayed infusion reactions in all subjects who receive daratumumab:

- Oral corticosteroid (20 mg methylprednisolone or equivalent) on the first and second day after all infusions (if no infusion-related reaction is observed after the first 3 infusions, then postinfusion corticosteroids should be administered per investigator discretion)

For subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD) the following postinfusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their spirometry test (FEV1) should be performed before discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all infusions. If no infusion-related reaction has occurred, the follow-up telephone call 48 hours after the infusion is not required. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major infusion-related reactions, then these postinfusion medications may be waived after 4 doses at the investigator's discretion.

Any postinfusion medication will be administered after the infusion has completed.

Refer to Section 6.3.6 for additional details on the management of infusion reactions.

6.3.4. Daratumumab Dosing Delay and Modification

Dose modification of daratumumab is not permitted. Dose delay is the primary method for managing daratumumab-related toxicities.

6.3.5. Daratumumab Toxicity Management

Cycle Delays

On the first day of each new treatment cycle and before each daratumumab dose, the subject will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to NCI-CTCAE, Version 4.03. Dose delays will be based on the toxicity experienced during the previous infusion or newly encountered on Day 1 of a new cycle.

To allow for recovery from toxicity, the study treatment must be held if any of the following criteria are met, regardless of relationship to daratumumab.

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 or thrombocytopenia with (any grade) bleeding
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days

- Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
- Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception of Grade 2 laryngeal edema or Grade 2 bronchospasm, which must be fully recovered. If daratumumab administration does not commence within the prespecified window (Table 5) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 5: Daratumumab-Related Toxicity Management

Cycles	Frequency	Dose Held	Dosing Re-start
1 and 2	Weekly (q1wk)	>3 days	next planned weekly dosing date
3 to 6	Biweekly (q2wks)`	>1 week	next planned biweekly dosing date
7+	Every 4 weeks (q4wks)	>2 weeks	next planned every 4 weeks dosing date

Doses of daratumumab may be delayed up to 4 weeks (Cycle 1 to Cycle 6) or up to 6 weeks (Cycle 7 and beyond). If Day 1 of a cycle is delayed, Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should **not** be adjusted. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) will result in permanent discontinuation of daratumumab. If a dose delay occurs, then pharmacokinetic and pharmacodynamic assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.

A daratumumab dose that is held for more than the permitted time (Table 5) from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the sponsor at the earliest possible time. Subjects whose dose was delayed for more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.3.6. Guidelines for Daratumumab Infusion-Related Reactions

Subjects should be carefully observed during infusions.

Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions, and resources necessary for resuscitation must be available. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of daratumumab (see Table 6).

Table 6: Management of Daratumumab Infusion-related Reactions

Severity [per CTCAE 4.03]	Recommended action
Grade 1 or Grade 2	• Interrupt infusion and manage symptoms • Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. • If patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate as outlined in Table 3.
Grade 3	• Interrupt infusion and manage symptoms • Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. • If the subject does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 3. • Repeat the procedure above in the event of recurrence of Grade 3 symptoms. • Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion-related reaction.
Grade 4	• Permanently discontinue daratumumab treatment and manage symptoms

7. TREATMENT COMPLIANCE

Talacotuzumab and daratumumab will be administered by qualified site staff, and each administration will be recorded in the eCRF. Following Amendment 4 and either 1 year after the last subject is randomized or anytime the sponsor terminates the study (whichever occurs first), the eCRFs will be closed.

8. PRESTUDY AND CONCOMITANT THERAPY

8.1. Prestudy Therapy

Prestudy MDS therapies administered up to 30 days before first dose of study drug must be recorded at screening. Transfusions up to 16 weeks prior to randomization also must be recorded at screening.

8.2. Concomitant Medications

Subjects should receive supportive care as clinically indicated. This includes blood product support (blood transfusions and use of granulocyte colony stimulating growth factors), anti-diarrheals, anti-emetics, analgesics, anti-infective treatment, and treatment of other medical conditions.

The following medications are prohibited during the study: ESA therapy, chemotherapy (anticancer), immunomodulatory drugs, immunotherapy, experimental therapy, and radiotherapy. Systemic use of corticosteroids in excess of prednisone 20 mg/day or its equivalent for more than

10 days is prohibited unless reviewed and approved by the sponsor. Long-term, chronic use of corticosteroids at any dose should also be reviewed and approved by the sponsor. Corticosteroids used as premedication are permitted. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

All concomitant therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements), including growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), corticosteroids, anti-arrhythmics and other cardiac supportive therapy, anti-histamines, anti-emetics, anti-diarrheals, and anti-coagulants must be recorded throughout the study beginning with signing of the ICF to 30 days after the end of dosing or until the start of subsequent anticancer treatment, if earlier. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study. Concomitant therapies should be recorded beyond 30 days after the last dose of study treatment only in conjunction with new or worsening adverse events or serious adverse events that meet the criteria outlined in Section 12.3.2, Serious Adverse Events. The follow-up of subjects in the study and study data collection will end either 1 year after the last subject is randomized or anytime the sponsor terminates the study. Subjects who are continuing to derive benefit from daratumumab treatment as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data collection has ended, only serious adverse events will be monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedule.

9. STUDY EVALUATIONS

The follow-up of subjects in the study and study data collection will end either 1 year after the last subject is randomized or anytime the sponsor terminates the study. Subjects who are continuing to derive benefit from daratumumab treatment as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data collection has ended, only serious adverse events will be monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedule.

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarize the frequency and timing of efficacy, PK, immunogenicity, biomarker, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECG, vital signs/physical exam, bone marrow assessments/clinical laboratory assessments/peripheral blood sampling for central lab submission, response assessment and other subject review data collection, study drug administration. Blood collections for PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

The total blood volume to be collected from each subject will be approximately 330 mL for subjects completing 8 cycles. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

An indwelling intravenous cannula may be used for blood sample collection. If a mandarin (obturator) is used, blood loss due to discard is not expected.

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. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

9.1.2. Screening Phase

Screening procedures will be performed within 28 days before randomization, as described in the Time and Events Schedules.

9.1.3. Open-Label Treatment Phase

The Treatment Phase will begin on Day 1 of Cycle 1 and will continue until discontinuation of study drug.

Treatment Phase

A treatment cycle is defined as 28 days. Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedules. Subjects will be monitored for adverse events, laboratory abnormalities, hematologic improvement, reduction in transfusion requirement, and clinical response. All Treatment Phase visit procedures are to be performed predose, unless otherwise specified, and laboratory test results must be reviewed prior to administering study drug. Adverse events and changes to concomitant medications will be recorded. The investigator will assess subject response to therapy using the efficacy measurements and disease response criteria according to the IWG 2006 (Attachment 6). If a subject develops features of response (eg, recovery from all cytopenias) and CR or PR are clinically suspected at a time not specified on the Time and Events Schedules, then all required disease assessments should be performed. In order to confirm a CR or PR per IWG 2006 criteria, all disease assessments including bone marrow aspirate should be repeated 4-8 weeks from time of CR or PR. If progressive disease is diagnosed, or the subject discontinues study drug for other reasons, then the subject will complete the End-of-Treatment Visit within 30 days after the last dose of study drug, and enter the Posttreatment Follow-up Phase.

End of Treatment/Early Withdrawal

An End-of-Treatment Visit will be scheduled within 30 days after the last dose of study drug for all subjects, including those who discontinued study drug for any reason, except for those lost to follow-up, death, or withdrawal of consent for study participation. Subjects who discontinued study drug due to disease progression, adverse event, lack of response, or other reasons and enter the Posttreatment Follow-up Phase should have the End-of-Treatment Visit completed before starting any subsequent MDS treatment. If a subject is unable to return to the site for the End-of-

Treatment Visit, then the subject should be contacted to collect adverse events that occur within 30 days after the last dose of the last study drug. Additional information on reporting adverse events may be found in Section 12.3.1.

9.1.4. Posttreatment Phase (Follow-Up)

The Posttreatment Follow-up Phase is the time between the End-of-Treatment Visit and the end of study participation or end of study. Subjects who are continuing to derive benefit from treatment as assessed by their investigator will continue to receive treatment and be monitored for safety by the sponsor.

During this phase, contact will be made as detailed in the Time and Events Schedules every 16 weeks.

If the information on survival status and subsequent therapy 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. Where allowed by local law, public records may be used to document death for the purpose of obtaining survival status.

9.1.5. Clinical Cutoff and End of Study

The clinical cutoff for the purpose of primary endpoint analysis is 6 months after randomization of the last subject.

The end of study data collection is defined as either 1 year after the last subject is randomized or anytime the sponsor terminates the study. At that time, study follow-up of subjects and study data collection will end. Subjects who are continuing to derive benefit from daratumumab treatment as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data collection has ended, only serious adverse events will be monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedule.

9.2. Efficacy Evaluations

Efficacy evaluations will include transfusion data, blood count assessments, and bone marrow biopsy and aspirate for disease assessment.

9.2.1. Transfusions

Data to be collected at each visit include the number of units and type of blood products transfused and the pre-transfusion hemoglobin and platelet count. Transfusion data will be collected during the treatment and posttreatment periods as specified in the Time and Event Schedules. Transfusion is monitored at each visit for infusion (every 4-week cycle), at each disease evaluation visit, and at all unscheduled visits during treatment. During the posttreatment phase, transfusion data will be collected every 4 to 6 weeks. Specific operational monitoring will be implemented to seek transfusion information from other documented sources. Specific and continuous medical review will be implemented to identify any sudden but unsustained increase

of Hb values and to query whether transfusion has occurred. Red blood cell transfusions may be administered based on hemoglobin level (sponsor should be notified for Hb >11 g/dL), investigator's assessment of the subject's clinical signs and symptoms, and local clinical practice.

As the volume of 1 unit of RBC transfusion may vary regionally, 1 unit is defined as the amount that is intended to raise Hb by approximately 1 g/dL in an adult patient (ie, 1 standard pRBC unit or equivalent). The total number of RBC units required over consecutive 8-week time periods will be calculated to identify subjects who achieve RBC TI or transfusion reduction.

9.2.2. Hemoglobin Assessment

Hemoglobin levels will be measured weekly during the first 8 weeks, at the start of each cycle, and as clinically needed.

For a given subject, the same local laboratory should be used for each hematology assessment throughout the study, to the extent possible. Hematologic improvement-erythroid response (HI-E) is defined as a Hb rise of at least 1.5 g/dL above baseline, measured 28 days or more following the last RBC transfusion or reduction of at least 4 units of RBC transfusions/8 weeks compared with the 8 weeks prior to start of treatment (criterion adapted from IWG 2006).

9.2.3. Clinical Bone Marrow Assesment

Bone marrow aspirate and biopsy must be performed during screening or up to 12 weeks before randomization. Follow-up bone marrow exams will be performed every 24 weeks, at the time of PR and CR (as indicated by peripheral blood counts), at disease progression, and at end-of-treatment. Following the bone marrow exams at PR and CR, bone marrow sampling should be repeated 4 to 8 weeks later. Bone marrow sampling does not have to be repeated at the End-of-Treatment visit if the prior assessment occurred within 8 weeks.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Sample Collection and Handling

For all subjects in the talacotuzumab or daratumumab treatment groups, PK samples to determine serum concentration of talacotuzumab or daratumumab will be obtained according to the Time and Events Schedules.

Venous blood samples (5 mL per sample) will be collected to determine serum concentration of talacotuzumab or daratumumab. The serum will be divided into 3 aliquots: 1 aliquot for PK analyses for talacotuzumab or daratumumab, 1 aliquot for anti-talacotuzumab or anti-daratumumab antibodies assessment (when appropriate), and 1 aliquot as a backup. Samples collected for determining serum concentrations of talacotuzumab or daratumumab in this study may be used to 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. In addition, samples will be collected at the time of an infusion-related reaction. Genetic analyses will not be performed on these samples.

The exact dates and times of blood sampling must be recorded. Refer to the laboratory manual or equivalent document for sample collection 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

Pharmacokinetics/Immunogenicity

Serum concentrations of talacotuzumab or daratumumab and detection and characterization of anti-talacotuzumab or anti-daratumumab antibodies will be performed using validated immunoassay methods by or under the supervision of the sponsor.

9.3.3. Pharmacokinetic Parameters

Serum concentrations of talacotuzumab or daratumumab will be measured and resulting concentration over time data will be summarized by treatment. Population PK models may be explored and developed if data are sufficient from this study and may include data from other studies.

The PK parameters are defined as:

C_{max} Maximum observed serum concentration

C_{min} Minimum observed serum concentration

If sufficient data are available, then pharmacokinetic/pharmacodynamics (PK/PD) modeling may be performed, including exploring the relationship between serum concentrations of talacotuzumab or daratumumab and biomarkers, PD markers, and endpoints of clinical efficacy, and may include data from other studies. If these analyses are performed, the details and results will be presented in a separate report.

9.3.4. Immunogenicity Assessments (Antibodies to Talacotuzumab and Daratumumab)

Serum from venous blood samples collected from all subjects will be assessed for the generation of antibodies to talacotuzumab or daratumumab (immunogenicity) according to Time and Events Schedules. Talacotuzumab or daratumumab concentration will be evaluated at all immunogenicity time points to ensure appropriate interpretation of immunogenicity data. When both serum concentration and immunogenicity analyses are specified for a particular timepoint, they are 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.

Additionally, blood samples to assess immunogenicity of either talacotuzumab or daratumumab should be collected at the final visit for subjects who discontinue treatment. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the Follow-up Phase.

Serum samples will be screened for antibodies binding to talacotuzumab or daratumumab 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.

A blood sample should be drawn, if possible, for determination of antibodies to talacotuzumab any time an infusion-related reaction is observed or reported during the study. 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 or daratumumab 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. 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 Schedules and will be analyzed at a central laboratory.

Assessment of Pharmacodynamic Markers (Basophils and pDC)

Previous clinical studies with talacotuzumab in patients with AML demonstrated that pDCs and basophils are reliable cellular PD markers for talacotuzumab activity, and that NK cells and monocytes are relatively stable in number from baseline during the treatment. Changes of cell numbers of cellular biomarkers (basophils, pDC, monocytes, eosinophils and NK cells) will be enumerated in the peripheral blood by flow cytometry.

Determination of CD123 and CD38 Expression

CD123 expression in various cell populations at baseline (bone marrow aspirate) will be determined by flow cytometry of MDSCs and MDS blasts, and CD38 expression will be analyzed in MDSCs and Tregs. CD123 expression of various cell populations listed above will also be analyzed in the peripheral blood and bone marrow throughout the study (see Time and Events Schedules). The diagnostic block for each patient will be requested to evaluate CD123 expression by immunohistochemistry (IHC) at a central laboratory. Upon disease progression, MDSCs (CD123 and CD38), blasts (CD123), and Tregs (CD38) will be evaluated.

Mutation Analysis

Some somatic mutations are known to confer a poor prognosis and resistance to certain forms of therapy. Therefore, baseline mutation status will be evaluated in the baseline bone marrow biopsy to explore potential inter-individual variability in clinical outcomes or identification of population subgroups that respond differently to either treatment.

Immunophenotyping and Calculating Baseline Frequencies

Whole blood will be utilized for immunophenotyping (performed by flow cytometry or mass cytometry/CyTOF), which includes analyses of NK cells, MDSCs, MDS blasts, and T cells as well as other potential immune cell subpopulations and their absolute numbers. The NK cells (CD45+CD56+CD3-) and their activation markers (CD16, CD314, and CD335) will be assessed by flow cytometry because the primary mechanism of action of talacotuzumab is antibody-dependent cellular cytotoxicity (ADCC) through NK cells.

Proteomic Analysis

Peripheral blood plasma will be analyzed for protein expression associated with disease progression or response to talacotuzumab or daratumumab.

9.5. Safety Evaluations

All subjects who receive at least one dose of talacotuzumab or daratumumab will be considered evaluable for safety. Any clinically relevant changes occurring during the study must be recorded in the Adverse Event section of the eCRF. Any serious adverse events 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. A sponsor safety review committee will review all the safety data on a quarterly basis, or ad hoc, as needed (see Section 11.9).

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedules:

Adverse Events

Adverse events (AEs) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study (ie, from the time of signing ICF until 30 days after the end of dosing or until the start of subsequent anticancer treatment, if earlier). Adverse events will be reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

The follow-up of subjects in the study and study data collection will end either 1 year after the last subject is randomized or anytime the sponsor terminates the study. Subjects who are continuing to derive benefit from daratumumab treatment after study data collection ends as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data collection has ended, only serious adverse events will be

monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedules.

Clinical Laboratory Tests

Required laboratory tests must be performed within 48 hours of the scheduled visit. For Cycle 1 Day 1 only, clinical laboratory tests do not need to be repeated if the Screening tests were performed within 5 days of the first dose of study treatment.

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. For example, laboratory abnormalities leading to an action regarding any study treatment (dose reduction, temporary stop, delay of the start of a cycle or permanent stop) or the start of concomitant therapy should be reported. For each laboratory abnormality reported as an adverse event, the following laboratory values should be reported in the laboratory section of the eCRF: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the adverse event, and the value supporting recovery to Grade ≤1 or to baseline values.

The following tests will be performed by the local laboratory at the timepoints shown in the Time and Events Schedules:

- **Hematology:** hemoglobin, platelet count, white blood cell count, manual absolute peripheral blast count, absolute neutrophil count (ANC)
- **Serum Chemistry:** Creatinine, total bilirubin (with fractionation if abnormal), ALT, AST, alkaline phosphatase (ALP), lactate dehydrogenase, albumin, serum EPO, serum ferritin, and transferrin saturation
- Serum β-hCG or urine pregnancy testing for women of childbearing potential only (screening only) or if clinically indicated or required by local regulations
- Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)

Electrocardiogram (ECG)

A 12-lead electrocardiogram will be performed in all subjects during Screening and on Day 1 of Cycle 1.

During the collection of ECG, 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 timepoint as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

ECOG Performance Status

The ECOG performance status scale will be used to grade changes in the subject's activities of daily living.

Vital Signs

Pulse and blood pressure will be recorded, preferably while the subject is seated, at the time points specified in the Time and Events Schedules. Vital signs that are considered to be clinically relevant by the investigator are to be documented as adverse events.

Physical Examination

Screening physical examination should include body weight, height, and the evaluation of head, eye, ear, nose, and throat; cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Only a limited symptom-directed physical examination and weight assessment is required on Day 1 of all cycles after baseline. New or worsened abnormalities should be recorded as adverse events if appropriate.

9.5.1. Indirect Antiglobulin Test (IAT)

Blood Type, Rh, and IAT should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion.

Daratumumab interferes with the Indirect Antiglobulin Test (IAT), which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT).[1]

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

a) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units
b) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the daratumumab Investigator's Brochure.[12]

9.5.2. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase for subjects enrolled in the daratumumab arm, as per institutional guidelines.

9.6. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the Time and Events Schedules for the timing and frequency of all sample collections. Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has died or has been lost to follow-up. All other subjects will be followed until the end of the study. The end of study data collection is defined as either 1 year after the last subject is randomized or anytime the sponsor terminates the study. At that time, study follow-up of subjects and study data collection will end. Subjects who are continuing to derive benefit from daratumumab treatment as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data collection has ended, only serious adverse events will be monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedule.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

If a subject's study drug must be discontinued, this will not result in automatic withdrawal of the subject from the study.

Discontinuation of Study Treatment

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject experiences disease progression or relapse
- The subject refuses further treatment
- A serious protocol violation has occurred, as determined by the principal investigator or the sponsor

End-of-treatment and posttreatment follow-up assessments should be obtained. The reason(s) a subject discontinues treatment will be recorded on the eCRF.

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 sponsor discontinues 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 before the end of the Treatment Phase, end-of-treatment and posttreatment follow-up assessments should be obtained, unless the subject withdraws consent.

10.3. Withdrawal From the Use of Research Samples

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 (SAP).

11.1. Subject Information

Efficacy and safety analyses will be performed using the Treated Population, which will include all subjects who received at least 1 dose of study drug.

The PK/PD evaluable population will consist of all subjects who received at least 1 dose of study drug and had at least 1 sample collected during treatment to determine the drug concentration or PD biomarker response. Continuous variables will be summarized using descriptive statistics such as mean, median, standard deviation, 25^{th} and 75^{th} percentiles, and range. Categorical variables will be summarized using frequency tables. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

11.2. Sample Size Determination

On the basis of historical data, the TI rate with treatment of best supportive care is expected to be approximately 2.5% in subjects with low or intermediate-1 risk MDS.[17] The primary objective is to evaluate the likelihood that treatment with talacotuzumab or daratumumab can result in a true TI rate ≥30%. A true TI rate ≤15% (6 times of the TI rate of best supportive care) will be considered as of no clinical interest in the context of this Phase 2 study. The number of subjects to be randomized into each arm will be 30, with which the lower boundary of the 2-sided 80% credible interval will exceed 15% if ≥8 (26.7%) subjects achieve TI. This sample size determination utilizes a Bayesian approach with *Beta(0.5, 0.5)* as the prior distribution and *Beta(0.5+**m**, 0.5+30-**m**)* as the posterior distribution for the true TI rate, where ***m*** is the observed number of subjects who achieve TI.

11.3. Efficacy Analyses

Primary Endpoint

The primary efficacy endpoint is RBC TI, lasting for at least 8 weeks.

There is no statistical hypothesis testing and no formal statistical comparison between the 2 arms.

Based on the observed number of subjects achieving TI (number of TIs), a Bayesian approach will be used to determine if the outcome of each treatment arm is "meeting" or "not meeting" the primary objective, or statistically "inconclusive." This statistical assessment will be used to guide decision making for further development of either or both compounds. The evaluation will be performed against the target value (TV) of 30% and the minimum acceptable value (MAV) 15% for the TI rate. The TV of 30% is defined according to study primary objective and is deemed clinically meaningful. A TI rate below 15%, the MAV, will be of no clinical interest. TI rates between MAV and TV will be considered modest, which will define a statistically inconclusive outcome. Operating characteristics (false positive and false negative error rates) of the statistical criteria are calculated using a Bayesian approach with *Beta(0.5, 0.5)* as the prior distribution and *Beta(0.5+**m**, 0.5+**30-m**)* as the posterior distribution of the true TI rate, where ***m*** is the observed number of TIs.

The TI rate point-estimate and corresponding 2-sided 80% credible interval (CI) will also be summarized for each treatment arm.

The above statistical inferences are summarized in the Table 7.

The lower boundary of the 2-sided 80% credible interval will exceed 15% (the MAV) if the observed number of TI is ≥8. If number of TIs is ≥13, then the outcome will be considered highly desirable as the lower boundary of the credible interval will exceed 30% (the TV). If the number of TIs is ≤5, then this will be an undesirable outcome as the upper bound of the credible interval is below 30%. When outcomes are statistically inconclusive (number of TI=6 or 7), results of additional sensitivity analyses and other endpoints (secondary, safety, PK, PD/biomarker) will play a more important role in decision making.

Table 7: Observed TI, 2-Sided Credible Interval, and Statistical Decision Criteria

Number (%) of Observed TI	80% CI[1]	"Meeting" Primary Objective
4 (13.3)	(7.1, 22.9)	No[2]
5 (16.7)	(9.6, 26.8)	
6 (20.0)	(12.2, 30.6)	Inconclusive
7 (23.3)	(14.8, 34.3)	
8 (26.7)	(17.6, 37.9)	Yes[3]
9 (30.0)	(20.4, 41.4)	
10 (33.3)	(23.3, 44.9)	
11 (36.7)	(26.2, 48.3)	
12 (40.0)	(29.2, 51.7)	
13 (43.3)	(32.3, 55.0)	
14 (46.7)	(35.4, 58.2)	

[1] Using *B(0.5, 0.5)* as the prior distribution for true IT rate
[2] With false negative error rate <10%; ie, when observing number of TI ≤5, there is a <10% chance that the true TI rate is ≥30%
[3] With false positive error rate <10%; ie, when observing number of TI ≥8, there is a <10% chance that the true TI rate is ≤15%

In addition to the aforementioned statistical assessments, sensitivity analyses will also be performed for the primary endpoint. In these analyses, additional subjects will also be considered transfusion independent if they are transfusion-free for less than 8 weeks but have maintained such a status for at least 6 consecutive weeks (42 days) by the time of the clinical cutoff (6 months after last randomization).

Secondary Endpoints

The proportion of subjects with TI lasting at least 168 days (24 weeks), CR, PR, and HI will be summarized descriptively.

The distributions of time to TI, and duration of TI will be estimated for each treatment arm using Kaplan-Meier method. These analyses will be based on subjects who achieve TI.

Other time-to-event endpoints including OS and time to progression to AML will be analyzed using Kaplan-Meier methods.

11.4. Pharmacokinetic Analyses

Data for all subjects who have sufficient and interpretable data for treatment with talacotuzumab or daratumumab will be included in both the PK and the PD analysis. Descriptive statistics (geometric and arithmetic means, standard deviation, and coefficient of variation [%]) will be provided to summarize serum concentrations of talacotuzumab or daratumumab at each sampling time point and PK parameters such as: C_{max} and C_{min} as appropriate.

Pharmacokinetic analyses will be performed on the PK-evaluable population, defined as subjects who have received at least 1 dose of talacotuzumab or daratumumab and have at least 1 postinfusion sample.

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. The number of subjects and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Descriptive statistics will be used to summarize talacotuzumab or daratumumab serum concentrations at each sampling time point. C_{min} is defined as the minimal concentration observed immediately before infusion and C_{max} is defined as the maximum concentration observed at the end of infusion, as presented in the summary of serum concentration by sampling timepoint. Other PK parameters, if available, may also be summarized.

If sufficient data are available, population-PK analysis of serum concentration-time data of talacotuzumab or daratumumab may be performed and may be combined with data from other studies. If the population-PK analysis is conducted, details will be given in a population-PK analysis plan and the results of the analysis will be presented in a separate report.

11.5. Immunogenicity Analyses

The incidence of anti-talacotuzumab and anti-daratumumab antibodies will be summarized for all subjects who receive at least 1 dose of talacotuzumab and daratumumab and have appropriate samples for detection of antibodies to talacotuzumab and daratumumab (ie, subjects with at least 1 sample obtained after their first dose of talacotuzumab and daratumumab). A listing of subjects positive for anti-talacotuzumab or anti-daratumumab antibodies will also be presented.

11.6. Biomarker Analyses

Biomarker measures and the change from baseline will be listed, tabulated, and plotted where appropriate. Subjects may be grouped by treatment, biomarker subgroups, or clinical response. Correlation of baseline or changes of biomarkers with clinical parameters will be analyzed by appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate).

Results of biomarker analyses may be presented in a separate report. Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information.

11.7. Pharmacokinetic/Pharmacodynamic Analyses

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

11.8. Safety Analyses

Safety analyses will be performed using the Treated Population. Safety will be evaluated using the NCI-CTCAE (Version 4.03). The safety parameters to be evaluated are the incidence, intensity, and type of adverse events, clinically significant changes in the subject's physical

examination findings, vital signs measurements, clinical laboratory results (hematology and chemistry), and deaths. Exposure to study treatment and reasons for discontinuation will be tabulated.

Adverse Events

Treatment-emergent adverse events are adverse events that occur after the first dose of study drug through 30 days following the last dose of study drug; any adverse event considered study drug-related regardless of the start date of the event; or any event that is present at baseline but worsens in severity or is subsequently considered drug-related by the investigator. Treatment-emergent adverse events will be summarized by System Organ Class and preferred term, by intensity (NCI-CTCAE, Version 4.03), and by drug relationship.

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

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 included in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. A summary of the shifts in selected laboratory hematology and serum chemistry parameters from baseline to the worst toxicity grade during the study will be provided. The worst toxicity grade during the study will be tabulated.

Electrocardiogram

Electrocardiogram data will be listed.

Vital Signs

Descriptive statistics of temperature, heart rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

11.9. Safety Review

A sponsor safety review committee will review all the safety data on a quarterly basis, or ad hoc, as needed. Committee members include study team clinicians and company safety officer.

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.

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 daratumumab, 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, Attribution Definitions.

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/SAE should be completed using the NCI-CTCAE Version 4.03. Any adverse event/SAE not listed in the NCI-CTCAE will be graded by the investigator 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 or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational 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)
- Exposure to a sponsor study drug from breastfeeding

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

12.3. Procedures

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 completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, and those that are considered related to study treatment occurring within the Follow-up Phase, 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.

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. Anticipated events will be recorded and reported as described in Attachment 9.

The follow-up of subjects in the study and study data collection will end either 1 year after the last subject is randomized or anytime the sponsor terminates the study. Subjects who are continuing to derive benefit from daratumumab treatment as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data collection has ended, only serious adverse events will be monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedule.

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). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

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

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 course 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.

- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/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).

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

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.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

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 in 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 in 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 (JNJ-56022473) is supplied for this study 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 daratumumab supplied for this study is a colorless to yellow liquid and sterile concentrate of 20 mg/mL as a liquid vial. Both will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

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

All study drug must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from exposure to light.

Daratumumab product must be stored in the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C. Study drug must not be utilized after the expiry date printed on the label. The daratumumab product must be protected from light and must not be frozen. Daratumumab does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

Refer to the study site investigational product and procedures 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, and study drug returned by the subject, 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, or used returned study drug for destruction, 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.

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. Returned study drug must not be dispensed again, even to the same subject. 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.

The end of study data collection is defined as either 1 year after the last subject is randomized or anytime the sponsor terminates the study. At that time, study follow-up of subjects and study data collection will end. Subjects who are continuing to derive benefit from daratumumab treatment as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data collection has ended, only serious adverse events will be monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedule.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study Protocol
- Investigator's Brochures Package Insert for Daratumumab
- Pharmacy manual/study site investigational product manual
- Laboratory manual
- NCI-CTCAE Version 4.03
- IVRS/IWRS Manual

- Electronic data capture (eDC) Manual
- Sample ICF

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is a proof-of-concept study that evaluates talacotuzumab and daratumumab as separate agents in subjects with low risk MDS. There is an unmet need for agents that relieve the transfusion requirements, mostly RBC, for subjects with low-risk MDS. Preclinical evidence suggests that these agents may promote normal hematopoiesis in the bone marrow by elimination of immune suppressor cells and potentially improve TI. Talacotuzumab is currently being evaluated in a Phase 2 study in patients with AML, a myeloid disease closely related to MDS and is considered safe and tolerable at the dose specified in this protocol. Daratumumab has been approved in the US and EU for the treatment of patients with relapsed and refractory multiple myeloma under the regimen specified in this protocol. In the AML and MM indications, the health of patients is likely to be more compromised than for patients with low-risk MDS. The sponsor considers the potential clinical benefits to outweigh the known risks of talacotuzumab or daratumumab treatment for patients with low-risk MDS.

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.

Treatment allocation is randomized therefore patients have equal chances of receiving either of the 2 experimental treatments. Patients will undergo the same procedures and testing regardless of which treatment that they receive. As a precautionary measure, due to benefit / risk considerations for patients with low-risk MDS, enrollment to the talacotuzumab arm has been closed based upon the occurrence of a Grade 4 infusion-related reaction in the first subject to receive talacotuzumab. The IWRS was modified to only permit enrollment to the daratumumab arm of the study.

Infusion-related reactions are associated with both agents. Several safeguards, including premedication regimens for both agents as well as postmedications for daratumumab, are mandated to reduce the occurrence or the severity of infusion-related reactions.

Because of the cytopenias associated with MDS, routine hematology values will be monitored.

The follow-up of subjects in the study and study data collection will end either 1 year after the last subject is randomized or anytime the sponsor terminates the study. Subjects who are continuing to derive benefit from daratumumab treatment as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data

collection has ended, only serious adverse events will be monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedule.

The total blood volume to be collected is considered to be an acceptable amount of blood for subjects participating in an MDS clinical study and is deemed reasonable over this time period in this study.

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 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.

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

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.

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 PD, biomarker, PK 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 talacotuzumab and daratumumab, to understand MDS, to understand differential drug responders, and to develop tests/assays related to talacotuzumab and daratumumab and MDS. 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 10.3, Withdrawal From the Use of Research Samples.

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 16.1, 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 IEC/IRB (where required) only needs to be notified.

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

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.

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

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

The minimum source documentation requirements for Section 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. If the electronic source system is utilized, references made to the eCRF 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 eCRF. 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 eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic 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 eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRF 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.

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

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

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, and periodic monitoring visits by the sponsor[, and direct transmission of biomarker, immunogenicity and PK data from central laboratories into the

sponsor's data base. 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 eCRFs 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 CRF 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 use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF 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 CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The end of study data collection is defined as 1 year after last subject has been randomized or anytime the sponsor terminates the study (see Section 17.9.2). At that time, study follow-up of subjects and study data collection will end. Subjects who are continuing to derive benefit from daratumumab treatment as assessed by their investigator may continue to receive daratumumab according to the protocol. During this period after study data collection has ended, only serious adverse events will be monitored and only entered into the company safety repository as described under Amendment 4 and in the Time and Events Schedule.

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 daratumumab 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 exploratory or 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 daratumumab, 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 exploratory or 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 disclose the existence of and the results of clinical studies as required by law.

REFERENCES

1. Chapuy, C, Nicholson R, Aguad MD, et al. Resolving the daratumumab interference with blood compatibility testing. Transfusion. 2015; 55:1545-1554.
2. Chen X, Eksioglu EA, Zhou J, et al. Induction of myelodysplasia by myeloid-derived suppressor cells. J Clin Invest. 2013 Nov;123(11):4595-611.
3. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-5.
4. Fenaux P, Ades L. How we treat lower-risk myelodysplastic syndromes. Blood. 2013;121(21):4280-6.
5. Garcia-Manero G, Jabbour E, Borthakur G, et al. Randomized open-label phase II study of decitabine in patients with low- or intermediate-risk myelodysplastic syndromes. J Clin Oncol. 2013;31(20):2548-53.
6. Gleason MK, Ross JA, Warlick ED, et al. CD16xCD33 bispecific killer cell engager (BiKE) activates NK cells against primary MDS and MDSC CD33+ targets. Blood. 2014;123(19):3016-3026.
7. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-88.
8. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012; 120: 2454-65.
9. Harnan S Association between transfusion status and overall survival in patients with myelodysplastic syndromes: A systematic literature review and meta-analysis. Acta Haematol 2016:136:23-42.
10. Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Br J Haematol. 2003;120(6):1037-46.
11. Hoechst B, Voigtlaender T, Ormandy L et al. Myeloid derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the NKp30 receptor. Hepatology 2009.
12. Investigator Brochure: JNJ-54767414 (daratumumab) Edition 12. Janssen Research & Development (06 October 2015).
13. Investigator Brochure: JNJ-56022473 (talacotuzumab) Edition 5. Janssen Research & Development (01 July 2016).
14. Kahn, J. D., Chamuleau, M. E., Westers, T. M., Van de Ven, P. M., van Dreunen, L., van Spronsen, M., Ossenkoppele, G. J., and van de Loosdrecht, A. A. (2015) Regulatory T cells and progenitor B cells are independent prognostic predictors in lower risk myelodysplastic syndromes. Haematologica 2014;100, e220-222.
15. Kelaidi C, Park S, et al. Long-term outcome of anemic lower-risk myelodysplastic syndromes without 5q deletion refractory to or relapsing after erythropoiesis-stimulating agents. Leukemia. 2013 Jun;27(6):1283-90.
16. Kordasti, S. Y., Ingram, W., Hayden, J., Darling, D., Barber, L., Afzali, B., Lombardi, G., Wlodarski, M. W., Maciejewski, J. P., Farzaneh, F., and Mufti, G. J. (2007) CD4+CD25high Foxp3+ regulatory T cells in myelodysplastic syndrome (MDS). Blood 2007; 110, 847-850.
17. Krejcik, J., Casneuf, T., Nijhof, I. S, et al. (2016) Daratumumab depletes CD38+ immune-regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood. Epub ahead of print.
18. Li L, Tao J, Fu R, Wang H, et al. Increased CD34+C38-CD123+ cells in Myelodysplastic syndrome displaying malignant features similar to those in AML. Int J Hematol (2014) 100:60-69.
19. Porter JB New insights into transfusion-related iron toxicity: implications for the oncologist Critical reviews in oncology/hematology 2016:99:261-271.
20. Raza A, Reeves JA, Feldman EJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. Blood. 2008; 111(1):86-93.

21. Santini V, Almeida A, Giagounidis A, et al. Randomized phase III study of lenalidomide versus placebo in RBC-transfusion dependent patients with lower-risk non-del(5q) myelodysplastic syndromes ineligible for or refractory to erythropoiesis-stimulating agents. J Clin Oncol. 2016;34:2988-2996.

22. Saunthararajah Y, Skeres M, Advani A, et al. Evaluation of cytotoxic DNMT1-depleting therapy in patients with myelodysplastic syndromes. J Clin Invest. 2015;125(3):1043–55.

23. Testa U, Riccioni R, Militi S, Coccia E, Stellacci E, Samoggia P,et al. Elevated expression of IL-3Ra in acute myelogenous leukemiais associated with enhanced blast proliferation, increasedcellularity, and poor prognosis. Blood. 2002;100:2980–8.

24. Tobiasson M, Dybedahl I, Holm MS, et al. Limited clinical efficacy of azacitidine in transfusion-dependent, growth factor-resistant, low- and Int-1-risk MDS: Results from the nordic NMDSG08A phase II trial. Blood Cancer J 2014;4,e189;doi:10,1038/bcj.2014.8.

25. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009, 114 (5) 937-51.

26. Yue L, Shao Z. Multi-parameter diagnosis of myelodysplasticsyndrome. Chin J Pract Intern Med. 2010;30(5):389–92.

27. Yue LZ, Fu R, Wang HQ, Li LJ, Shao ZH. Expression of CD123and CD114 on the bone marrow cells of patients with myelodysplastic syndrome. Chin Med J (Engl). 2010;123(15):2034–7.

Attachment 1: World Health Organization (WHO) Classification

Once a diagnosis of myelodysplastic syndrome (MDS) is established, 8 subtypes of MDS are recognized in the WHO classification that are distinguished by the percentage of myeloblasts, the presence of ringed sideroblasts, the number of dysplastic lineages, and karyotype as summarized in the following table:

MDS Subtype	Findings: Peripheral Blood	Findings: Bone Marrow
Refractory anemia (RA)	Anemia No or rare blasts	Erythroid dysplasia *only* <5% blasts <15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	Erythroid dysplasia *only* >15% ringed sideroblasts <5% blasts
Refractory cytopenia with multi-lineage dysplasia (RCMD)	Cytopenias (bi- or pancytopenia) No or rare blasts No Auer rods <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in 2 or more myeloid cell lines <5% blasts in marrow No Auer rods <15% ringed sideroblasts
Refractory cytopenia with multi-lineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bi- or pancytopenia) No or rare blasts No Auer rods <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in 2 or more myeloid cell lines ≥15% ringed sideroblasts <5% blasts No Auer rods
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias <5% blasts No Auer rods <1 x 10$_9$/L monocytes	Uni-lineage or multi-lineage dysplasia 5% to 9% blasts No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias <5% to 19% blasts Auer rods ± <1 x 10^9/L monocytes	Uni-lineage or multi-lineage dysplasia 10% to 19% blasts Auer rods ±
Myelodysplastic syndromes, unclassified (MDS-U)	Cytopenias No or rare blasts No Auer rods	Uni-lineage dysplasia in granulocytes or megakaryocytes <5% blasts No Auer rods
Myelodysplastic syndromes associated with isolated del(5q)	Anemia <5% blasts Platelets normal or increased	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts No Auer rods Isolated del(5q)

SOURCE: Brunning RD, Bennet JM, Flandrin G, et al. Myelodysplastic Syndromes. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001:61-73.

Attachment 2: International Prognostic Scoring System (IPSS) for Myelodysplastic Syndrome

Prognostic Variable	Survival and AML Evolution Score Value				
	0	0.5	1.0	1.5	2.0
Marrow Blasts (%)	<5	5 to 10	n/a	11 to 20	21 to 30
Karyotype[a]	Good	Intermediate	Poor	N/A	N/A
Cytopenias: Neutrophil count <1800/µL Platelets <100,000/µL Hemoglobin <10 g/dL	0 or 1	2 or 3	N/A	N/A	N/A

a Good: normal or any one of the following: -Y, del 5q, del 20q; Intermediate: any other abnormality; Poor: chromosome 7 abnormalities, complex, ≥3 abnormalities

N/A = not applicable.

Risk Category:	Combined Score (Sum of Marrow Blast + Karyotype + Cytopenia Score)
Low	0
Intermediate-1	0.5 to 1.0
Intermediate-2	1.5 to 2.0
High	≥2.5

SOURCE: Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088.

Attachment 3: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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

SOURCE: Eastern Cooperative Oncology Group (ECOG). http://ecog.dfci.harvard.edu/general/perf_stat.html

Attachment 4: NYHA Classification

The Stages of Heart Failure – New York Heart Association (NYHA) Classification

Class	Subject Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath) .
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Heart Failure Society of America The Stages of Heart Failure – NYHA Classification. Available at http://www.hfsa.org/hfsa-wp/wp/stages-of-heart-failure/

Attachment 5: Asthma Guidelines

Components of Severity		Classification of Asthma Severity											
		Intermittent			Persistent								
					Mild			Moderate			Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Impairment	Symptoms	≤ 2 days/week			≥ 2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤ 2x/month		1-2x/ month	3-4x/month		3-4x/ month	> 1x/week but not nightly		> 1x/ month	Often 7x/week	
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/ week but not daily, and not more than 1x on	Daily			Several time per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
Normal FEV_1/FVC : 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Lung function FEV1 FEV1/FVC	N/A	Normal FEV_1 between exacerbations > 80% > 85%	Normal FEV_1 between exacerbations > 80% Normal	N/A	> 80% > 80%	> 80% Normal	N/A	60-80% 75-80%	60-80% Reduced	N/A	< 60% < 75%	< 60% Reduced
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.											

Recommended Step for Initiating Treatment	Step 1	Step 2	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
	In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.							

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Attachment 6: International Working Group (IWG) Response Criteria 2006

PROPOSED MODIFIED INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR ALTERING NATURAL HISTORY OF MDS

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

∗ Dysplastic changes should consider the normal range of dysplastic changes (modification).
† Modification to IWG response criteria.
‡ In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Proposed modified International Working Group response criteria for hematologic improvement

Hematologic Improvement*	Response criteria (responses must last ≥8 weeks)†
Erythroid response (pretreatment, <11 g/dL)	Hb increase by ≥1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hb of ≤9 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, <100 x 10^9/L)	Absolute increase of ≥30 x 10^9/L for patients starting with >20 x 10^9/L platelets Increase from <20 x 10^9/L to >20 x 10^9/L and by at least 100%†
Neutrophil response (pretreatment, <1 x 10^9/L)	At least 100% increase and an absolute increase >0.5 x 10^9/L†
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hb by ≥1.5 g/dL Transfusion dependence

∗ Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥1 week apart (modification).
† Modification to IWG response criteria.
‡ In the absence of another explanation such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Notes: Deletions to the IWG response criteria are not shown. To convert hemoglobin levels (concentrations) from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Abbreviations: CR: complete remission; DFS: disease-free survival; FAB: French-American-British; Hb: hemoglobin; HI: hematologic improvement; IWG: International Working Group; MDS: myelodysplastic syndromes; PFS: progression-free survival; PR: partial remission; RBC: red blood cell

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

Attachment 7: Conversion Table for Glucocorticosteroid Dose

Generic Name	Oral or Intravenous Dose (mg)
Dexamethasone	0.75
Hydrocortisone	20
Methylprednisolone	4
Prednisolone	5
Prednisone	5

Attachment 8: The Family of Antihistamine Medications

The following antihistamines may be used for daratumumab preinfusion medication (including, but not limited to):

- Diphenhydramine
- Cetirizine
- Fexofenadine
- Loratadine
- Clemastine
- Dexchlorpheniramine
- Promethazine*

  * The IV use of promethazine should be avoided.

Attachment 9: 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:

Indication related

- Dyspnea
- Fatigue
- Malaise
- Asthenia
- Hemorrhage (with thrombocytopenia)
- Infection
- Cytopenias
  - Thrombocytopenia
  - Neutropenia
    - Febrile neutropenia
  - Leukopenia
  - Lymphopenia
  - Pancytopenia

Population Related

- Arrhythmia, Atrial fibrillation
- Cardiac failure congestive
- Myocardial infarction; Cerebrovascular accident

Reporting of Anticipated Events

All adverse events will be recorded in the eCRF 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.

INVESTIGATOR AGREEMENT

JNJ-56022473 (talacotuzumab) and JNJ-54767414 (daratumumab)
Clinical Protocol 56022473MDS2002 – Amendment 4

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): Ming Qi

Institution: Janssen Research & Development

Signature: [redacted] Date: 13 December 2018
(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.

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Status: Approved, Date: 13 December 2018