

**TAKEDA PHARMACEUTICALS
PROTOCOL**

Protocol Full Title:	A Phase 3, Multicenter, Open-Label, Randomized Trial to Compare the Efficacy and Safety of Elritercept versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes in ESA-naïve Adult Participants Who Require Red Blood Cell Transfusions
Sponsor Confidentiality Statement:	This document is a confidential communication of Takeda. Acceptance of this document constitutes the agreement by the recipient that no information contained herein will be published or disclosed without written authorization from Takeda. Furthermore, the information is only meant for review and compliance by the recipient, his or her staff, and applicable institutional review committee and regulatory agencies to enable conduct of the trial.
Protocol Number:	TAK-226-3001
Original Protocol:	Yes
Amendment Number:	Not Applicable
Amendment Scope:	Global
Compound Number(s):	TAK-226, (formerly KER-050)
Compound Name(s):	Elritercept
Trial Phase:	3
Acronym:	ELRISE MDS
Short Title:	A phase 3 trial comparing elritercept versus epoetin alfa for treatment of anemia due to lower-risk MDS in ESA-naïve adults who require RBC transfusions.
Sponsor Name and Address:	Takeda Development Center Americas, Inc. 500 Kendall Street Cambridge, MA 02142 USA
Regulatory Agency Identifier Number(s):	IND: 163,309 EU Trial Number: 2025-523544-12
Sponsor Approval Date:	The approval date is the latest of the approval dates included on the last page of this document with the electronic signatures.

Sponsor Signatories:

Electronic signatures of the following individuals are provided on the last page of this document.

Alexander Vorog, MD Senior Medical Director, Oncology Clinical Research
Meliessa Hennessy, MPH Senior Scientific Director, Oncology Clinical Research
Cong Li, PhD Associate Director, Statistics
Xiaofei Zhou, PhD Senior Director, Quantitative Clinical Pharmacology

Medical Monitor's and Sponsor's Responsible Medical Officer's Name and Contact Information are provided separately.

Report Serious Adverse Events within 24 hours, regardless of causal relationship to the investigational product via the email or fax provided separately.

TABLE OF CONTENTS

TAKEDA PHARMACEUTICALS PROTOCOL	1
TABLE OF CONTENTS.....	3
1.0 PROTOCOL SUMMARY	13
1.1 Protocol Synopsis.....	13
1.1.1 Primary and Secondary Objectives and Endpoints	13
1.1.2 Overall Design.....	15
1.2 Trial Schema	17
1.3 Schedule of Activities	18
2.0 INTRODUCTION	26
2.1 Purpose of Trial.....	26
2.2 Summary of Benefits and Risks.....	26
2.2.1 Benefit Summary.....	26
2.2.2 Risk Summary and Mitigation Strategy	27
2.2.2.1 Trial Intervention	27
2.2.2.2 Trial Procedures	27
2.2.2.3 Comparator Agent.....	28
2.2.3 Overall Benefit:Risk Conclusion.....	28
3.0 TRIAL OBJECTIVES, ENDPOINTS, AND ESTIMANDS	28
3.1 Primary Objective + Associated Endpoint and Estimand.....	28
3.2 Secondary Objectives + Associated Endpoints and Estimands	29
3.3 Safety Objective + Associated Endpoint	33
3.4 Exploratory Objectives + Associated Endpoints	33
4.0 TRIAL DESIGN	35
4.1 Description of Trial Design	35
4.1.1 Intervention Model	35
4.1.2 Trial Duration	35
4.1.3 Method of Assignment to Trial Intervention.....	36
4.1.4 Additional Description of Design.....	36
4.1.5 Participant Input Into Design.....	36
4.2 Rationale for Trial Design	36
4.2.1 Rationale for Intervention Model	36
4.2.2 Rationale for Duration.....	37
4.2.3 Rationale for Endpoints.....	37

4.2.3.1	Rationale for Disease and Hematologic Response Assessment Endpoints	37
4.2.3.2	Rationale for Secondary Endpoints and Additional Analyses	38
4.2.3.3	Exploratory Endpoint on Molecular Mutations including SF3B1	38
4.2.4	Rationale for IA	39
4.2.5	Rationale for Comparator	39
4.2.6	Rationale for Adaptive or Novel Trial Design	39
4.2.7	Other Trial Design Considerations	40
4.2.8	Rationale for Stratification	40
4.2.8.1	RBC Transfusion Burden at Baseline	40
4.2.8.2	RS Status at Baseline	40
4.2.8.3	Endogenous sEPO Level at Baseline	40
4.3	Access to Trial Intervention After EOT	41
4.3.1	Posttrial Access	41
4.3.2	Duration of Posttrial Access	41
4.4	Start of Trial and EOT	41
4.4.1	Start of Trial Definition	41
4.4.2	Other Key Trial Timepoints	41
4.4.3	Early Trial or Site Closure	42
4.4.4	EOT Definition	42
5.0	TRIAL POPULATION	42
5.1	Selection of Trial Population	42
5.2	Rationale for Trial Population	43
5.3	Inclusion Criteria	45
5.4	Exclusion Criteria	46
5.5	Lifestyle Considerations	49
5.6	Screen Failures	49
5.6.1	Screen Failure Categorization, Information Collection, and Other Procedures ..	49
5.6.2	Rescreening	50
6.0	TRIAL INTERVENTION AND CONCOMITANT THERAPY	50
6.1	Description of Trial Intervention	50
6.2	Rationale for Trial Intervention	51
6.3	Dosing and Administration	52
6.3.1	Elritercept Dosing	52
6.3.1.1	Elritercept Dosing Modification	53

6.3.1.2	Elritercept Dose Reduction	54
6.3.1.3	Elritercept Dose Up-Titration	54
6.3.1.4	Elritercept Up-Titration to a Higher Dose After Dose Reduction	55
6.3.2	Epoetin Alfa Dosing	55
6.3.2.1	Epoetin Alfa Dose Modification	56
6.3.2.2	Epoetin Alfa Dose Reduction.....	56
6.3.2.3	Epoetin Alfa Dose Up-Titration.....	57
6.3.2.4	Self Administration of Epoetin Alfa	58
6.4	Treatment of Overdose	59
6.4.1	Elritercept Overdose	59
6.4.2	Epoetin Alfa Overdose	60
6.5	Preparation, Handling, Storage, and Accountability	60
6.5.1	Preparation of Trial Intervention	60
6.5.2	Handling and Storage of Trial Intervention.....	60
6.5.3	Accountability of Trial Intervention.....	61
6.6	Participant Assignment, Randomization, and Blinding.....	62
6.6.1	Participant Assignment.....	62
6.6.2	Randomization and Stratification	62
6.6.3	Blinding and Unblinding	62
6.7	Trial Intervention Compliance	63
6.8	Concomitant Therapy.....	63
6.8.1	Prohibited Concomitant Therapy	63
6.8.2	Permitted Concomitant Therapy.....	64
6.8.2.1	RBC Transfusion.....	64
6.8.2.2	Platelet Transfusion.....	64
6.8.2.3	Iron Chelation Therapy	64
6.8.3	Rescue Therapy	65
6.9	Management of Clinical Events.....	65
6.9.1	Elritercept	65
6.9.1.1	Hypertension	65
6.9.1.2	ADA	65
6.9.2	Epoetin alfa.....	65
6.9.2.1	Hypertension	65
6.9.2.2	Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism	66

6.9.2.3	Increased Mortality and/ or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer	66
6.9.2.4	Seizures	66
6.9.2.5	Rise in Platelet Counts	66
6.9.2.6	Serious Allergic Reactions	66
6.9.2.7	Severe Cutaneous Reactions	66
6.9.2.8	Other Frequently Reported Adverse Reactions.....	67
7.0	DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT WITHDRAWAL FROM TRIAL	67
7.1	Discontinuation of Trial Intervention	67
7.1.1	Criteria for Permanent Discontinuation of Trial Intervention	67
7.1.2	Temporary Discontinuation or Interruption of Trial Intervention.....	68
7.1.2.1	Elritercept.....	68
7.1.2.2	Epoetin Alfa	69
7.1.3	Rechallenge	69
7.2	Participant Withdrawal From the Trial	69
7.3	Lost to Follow-Up.....	70
7.4	Trial Stopping Rules	70
8.0	TRIAL ASSESSMENTS AND PROCEDURES	70
8.1	Screening/Baseline Assessments and Procedures.....	70
8.1.1	Demographics, Medical History, and Medication History.....	71
8.1.1.1	Demographics	71
8.1.1.2	Medical History.....	71
8.1.1.3	Transfusion History.....	71
8.1.1.4	Prior and Concomitant Medications.....	73
8.1.1.5	Concomitant Procedures	74
8.1.1.6	Diagnostic Criteria/Disease Classification.....	74
8.1.1.7	Coagulation Panel	75
8.2	Efficacy Assessments and Procedures	75
8.2.1	Pretransfusion Assessments.....	75
8.2.1.1	Baseline Hgb Threshold for RBC Transfusions.....	75
8.2.1.2	Pretransfusion Assessments for RBC Transfusions	75
8.2.1.3	Pretransfusion Assessments for Platelet Transfusions	75
8.2.2	Transfusion Verification.....	76
8.2.3	MDS Disease Assessment	76

8.2.4	HRQoL Measures	78
8.2.4.1	EORTC QLQ-C30	79
8.2.4.2	FACT-An Anemia Scale	79
8.2.4.3	EQ-5D-5L	79
8.2.4.4	Transfusion Burden Assessment	80
8.2.4.5	PGI-S/PGI-C Items	80
8.2.5	Trial Assessments During Dose Delays	80
8.2.6	Posttreatment Follow-Up.....	81
8.2.6.1	Safety Follow-Up	81
8.2.6.2	Survival Follow-Up.....	82
8.3	Safety Assessments and Procedures	82
8.3.1	Physical Examination	82
8.3.2	Vital Signs	82
8.3.2.1	Weight and Height	83
8.3.3	ECGs and Echocardiograms	83
8.3.3.1	ECGs	83
8.3.3.2	Echocardiogram	83
8.3.4	Clinical Laboratory Assessments	83
8.3.4.1	Use of Local Versus Central Laboratories	83
8.3.4.2	Clinical Hematology	84
8.3.4.3	Clinical Chemistry and Urinalysis	85
8.3.5	Suicidal Ideation and Behavior Risk Monitoring	85
8.4	AEs and SAEs	86
8.4.1	Definitions of AE and SAE	86
8.4.1.1	AE Definition	86
8.4.1.2	SAE Definition.....	86
8.4.2	Time Period and Frequency for Collecting AE and SAE Information	87
8.4.3	Identifying AEs and SAEs.....	87
8.4.4	Recording of AEs and SAEs	88
8.4.4.1	Recording of AEs	88
8.4.4.2	Recording of SAEs.....	88
8.4.5	Follow-up of AEs and SAEs	88
8.4.6	Reporting of SAEs.....	89
8.4.7	Regulatory Reporting Requirements for SAEs	89
8.4.8	Serious and Unexpected Adverse Reaction Reporting.....	90

8.4.9	AEs of Special Interest	90
8.4.10	Disease-related Events or Outcomes Not Qualifying as AEs or SAEs	90
8.4.11	Special Situations	90
8.4.12	Product Complaints	91
8.5	Pregnancy and Postpartum Information.....	91
8.5.1	Participants Who Become Pregnant During the Trial	91
8.5.1.1	Reporting.....	91
8.5.1.2	Continued Trial Participation.....	92
8.5.1.3	Lactation.....	92
8.5.2	Participants Whose Partners Become Pregnant.....	92
8.6	Medical Device Product Complaints for Drug/Device Combination Products	92
8.7	Pharmacokinetics	92
8.8	Genetics.....	92
8.9	Biomarkers.....	93
8.9.1	Circulating Clinical Biomarkers.....	93
8.9.2	Exploratory Circulating Biomarkers	93
8.9.3	Exploratory Mutational Analyses.....	94
8.10	Immunogenicity Assessments.....	94
8.11	Medical Resource Utilization and Health Economics	95
9.0	STATISTICAL CONSIDERATIONS.....	95
9.1	Analysis Sets.....	95
9.2	Analyses Supporting Primary Objective(s)	96
9.2.1	Statistical Model, Hypothesis, and Method of Analysis	96
9.2.1.1	Primary Endpoint	96
9.2.2	Handling of Intercurrent Events of Primary Estimand(s).....	96
9.2.3	Handling of Missing Data	97
9.2.4	Sensitivity Analysis	97
9.2.5	Supplementary Analysis	97
9.2.6	Subgroup Analyses.....	97
9.3	Analysis Supporting Secondary Objectives.....	98
9.3.1	Other Secondary and Exploratory HRQoL Endpoints	99
9.3.2	PK Analyses	100
9.3.3	Immunogenicity Analyses	100
9.4	Analysis of Exploratory Objective(s)	100
9.4.1	Clinical and Translational Biomarkers.....	100

9.4.2	Healthcare Resource Utilization.....	100
9.5	Safety Analyses.....	100
9.6	Other Analyses.....	101
9.7	Interim Analyses	101
9.8	Primary, Secondary and Final Analyses	101
9.9	Sample Size Determination.....	102
9.10	Protocol Deviations.....	102
10.0	GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT	103
10.1	Regulatory and Ethical Considerations.....	103
10.1.1	Investigator Responsibilities	103
10.1.1.1	Introduction	103
10.1.1.2	List of Investigator Responsibilities	103
10.1.1.3	Investigator Consent to Use of Personal Information	105
10.1.1.4	Investigator Agreement.....	105
10.1.2	Sponsor Responsibilities	107
10.1.2.1	Serious Breach of Protocol or EU Clinical Trial Regulation.....	107
10.2	Committees	107
10.2.1	Steering Committee	107
10.2.2	DMC	107
10.3	Informed Consent Process	108
10.3.1	Informed Consent for Rescreening.....	109
10.3.2	Informed Consent for Use of Remaining Samples for Future Research	109
10.4	Data Protection.....	110
10.4.1	Participant Confidentiality.....	110
10.4.2	Responsibilities Following Termination or Suspension.....	110
10.4.3	Serious Data Breach Prevention and Reporting	111
10.5	Early Site Closure or Trial Termination	111
10.5.1	Decision Rights for Site Closure and Trial Termination.....	111
10.5.2	Criteria for Early Trial Site Closure	111
11.0	GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE.....	112
11.1	Quality Tolerance Limits	112
11.2	Data Quality Assurance	112
11.2.1	Sponsor or Designee Responsibilities for Data Quality Assurance	112

11.2.2	Investigator Responsibilities for Data Quality Assurance.....	112
11.3	Source Data	113
11.3.1	Introduction	113
11.3.2	Investigator Expectations for Source Data	113
11.3.3	Trial Monitor Expectations for Source Data	113
11.3.4	Definition of Source Data.....	113
12.0	APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY	114
12.1	Further Details and Clarifications on the AE Definition	114
12.1.1	Pretreatment Event Definition.....	114
12.2	Further Details and Clarifications on the SAE Definition	114
12.3	Severity	114
12.4	Causality	114
13.0	APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS	115
13.1	Contraception and Pregnancy Testing	115
13.1.1	Definitions Related to Childbearing Potential.....	115
13.1.1.1	Participants of Childbearing Potential	115
13.1.1.2	Participants of Male Birth Sex who are Fertile.....	115
13.1.2	Contraception	115
13.1.2.1	Highly Effective, Acceptable, and Unacceptable Contraception Methods.....	115
13.1.2.2	Duration of Contraception Use	116
13.2	Clinical Laboratory Tests.....	117
13.3	Publication and Clinical Trial Registration and Disclosure Policies	117
13.3.1	Publication Policy.....	117
13.3.2	Clinical Trial Registration and Disclosure	117
13.4	Country/Region-Specific Differences.....	117
13.5	Prior Protocol Amendments.....	117
14.0	APPENDIX: SAMPLE RETENTION AND USE	117
14.1	Sample Retention	117
14.2	Sample Use for Future Research Purposes	118
15.0	APPENDIX: RECORD RETENTION	118
15.1	Record Retention Responsibilities of the Investigator/Site	118
15.1.1	Records To Retain	118
15.1.2	Duration of Record Retention	119

15.2	Record Retention Responsibilities of the Sponsor.....	119
16.0	APPENDIX: METHODOLOGY AND ASSESSMENT CRITERIA	119
16.1	Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status	119
16.2	Myelodysplastic Syndromes World Health Organization Classification System (2016)	121
16.3	INTERNATIONAL PROGNOSTIC SCORING SYSTEM-REVISED (IPSS-R) CLASSIFICATION OF VERY LOW, LOW, OR INTERMEDIATE RISK DISEASE	123
16.4	INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR MYELODYSPLASTIC SYNDROMES	124
17.0	APPENDIX: GLOSSARY OF TERMS	126
17.1	Abbreviations	126
17.2	Definitions	129
18.0	APPENDIX: REFERENCES.....	130

LIST OF TABLES

Table 1.a	Primary Objective and Associated Endpoint	13
Table 1.b	Secondary Objectives and Associated Endpoints	13
Table 1.c	SoA (Treatment)	18
Table 1.d	SoA (Follow-up)	24
Table 3.a	Primary Objective and Associated Endpoint	28
Table 3.b	Estimand Framework for Primary Endpoint	29
Table 3.c	Secondary Objectives and Associated Endpoints	29
Table 3.d	Estimand Framework for Alpha Controlled Secondary Endpoints	31
Table 3.e	Safety Objective and Associated Endpoint	33
Table 3.f	Exploratory Objectives and Associated Endpoints	33
Table 6.a	Table of Trial Interventions	50
Table 6.b	Elritercept Dose Modification and Discontinuation Guidelines	53
Table 6.c	Dose Reduction and Escalation Guidelines	54
Table 6.d	Epoetin Alfa Dose Modification and Discontinuation Guidelines	56
Table 6.e	Epoetin Alfa Dose Reductions and Escalations	57
Table 8.a	Clinical Hematology Tests	84
Table 8.b	Clinical Chemistry Tests	85
Table 8.c	Clinical Urinalysis Tests	85
Table 8.d	Safety Reporting Timeframes	86

Table 8.e	Clinical Biomarker Assessments	93
Table 16.a	ECOG Scale for Performance Status	119
Table 16.b	Peripheral Blood and BM Findings and Cytogenetics of Myelodysplastic Syndromes (MDS)	121
Table 16.c	IPSS-R Prognostic Score Values	123
Table 16.d	IPSS-R Cytogenetic Risk Groups	123
Table 16.e	IPSS-R Prognostic Risk Categories/Scores	123
Table 16.f	Hematologic Improvement According to IWG Criteria (Cheson, 2006)	124
Table 16.g	Altering Natural History of MDS According to IWG Criteria for MDS (Cheson, 2006)	125

LIST OF FIGURES

Figure 1.a	Trial Schema	17
------------	--------------------	----

1.0 PROTOCOL SUMMARY

1.1 Protocol Synopsis

1.1.1 Primary and Secondary Objectives and Endpoints

Table 1.a Primary Objective and Associated Endpoint

Primary Objective	Primary Endpoint
To evaluate the efficacy of elritercept on red blood cell transfusion independence (RBC-TI) for a minimum 12-week period within 24 weeks with concurrent mean hemoglobin (Hgb) increase ≥ 1.5 g/dL compared to epoetin alfa.	Proportion of participants who are RBC-TI for any consecutive ≥ 12 -week period from Cycle 1 Day 1 (C1D1) through Week 24 with concurrent mean Hgb increase ≥ 1.5 g/dL from baseline.

Table 1.b Secondary Objectives and Associated Endpoints

Secondary Objective	Secondary Endpoint
Key Secondary Objective: To compare the effect of elritercept on RBC-TI for a minimum 16-week period within 24 weeks versus epoetin alfa.	Key Secondary Endpoint: Proportion of participants who are RBC-TI for any consecutive ≥ 16 -week period from C1D1 through Week 24.
Key Secondary Objective: To compare effect of elritercept on RBC-TI for a minimum 12-week period within 24 weeks versus epoetin alfa.	Key Secondary Endpoint: Proportion of participants who are RBC-TI for any consecutive ≥ 12 -week period from C1D1 through Week 24.
Key Secondary Objective: To compare the effect of elritercept on RBC-TI for a minimum 24-week period within 24 weeks versus epoetin alfa.	Key Secondary Endpoint: Proportion of participants who are RBC-TI for a consecutive 24-week period from C1D1.
To compare the effect of elritercept versus epoetin alfa on favorable fatigue response with absence of RBC transfusion between the end of Week 12 and the end of Week 24.	Proportion of participants who have a confirmed meaningful improvement in Functional Assessment of Chronic Illness (FACIT)-Fatigue scale score with no RBC transfusion between the end of Week 12 and the end of Week 24 among those with low baseline scores or who maintain a high FACIT-Fatigue scale score with no meaningful deterioration and no RBC transfusion between the end of Week 12 and the end of Week 24 among those with high baseline scores.
To compare effect of elritercept on hematological improvement-erythroid (HI-E) for a minimum 8-week and for a minimum 12-week period within 24 weeks and within 48 weeks versus epoetin alfa.	Proportion of participants who achieved HI-E for a minimum 8-week and for a minimum 12-week period through Week 24 and Week 48.
To compare the effect of elritercept on RBC-TI at multiple time periods: for a minimum 8-week period within 24 weeks, and for a minimum 24-week period within 48 weeks versus epoetin alfa.	Proportion of participants who are RBC-TI for a minimum consecutive 8-week period from C1D1 through Week 24, and for a minimum consecutive 24-week period through Week 48.
To compare time to achieve RBC-TI for a minimum 12 weeks and a minimum 16 weeks RBC-TI within	Time from date of first dose to first onset of achieving RBC-TI for minimum consecutive 12 weeks and for

CONFIDENTIAL

Table 1.b Secondary Objectives and Associated Endpoints

Secondary Objective	Secondary Endpoint
24 weeks for participants receiving elritercept versus epoetin alfa.	minimum consecutive 16 weeks through Week 24.
To compare the effect of elritercept on mean Hgb change through 24 and 48 weeks.	Mean Hgb change from baseline through Week 24 and through Week 48.
To compare duration of RBC-TI ≥ 12 weeks and ≥ 16 weeks RBC-TI achieved within 24 weeks for participants receiving elritercept versus epoetin alfa.	Maximum duration of RBC-TI for participants who achieved consecutive ≥ 12 weeks and ≥ 16 weeks of RBC-TI from C1D1 through Week 24.
To compare RBC transfusion burden during treatment for participants receiving elritercept versus epoetin alfa.	Total number and monthly average of packed red blood cells (pRBC) units received during treatment period.
To compare time to receive first RBC transfusion for participants receiving elritercept versus epoetin alfa.	Time from date of first dose to date of first RBC transfusion received during treatment period.
To compare time to achieve HI-E for a minimum 8 weeks within 24 weeks for participants receiving elritercept versus epoetin alfa.	Time from date of first dose to first onset of achieving HI-E for minimum consecutive 8 weeks through Week 24.
To compare the effect of elritercept versus epoetin alfa on health-related quality of life (HRQoL).	Proportion of participants with meaningful improvement in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (physical function, dyspnea, and fatigue), Functional Assessment of Cancer Therapy-Anemia (FACT-An), and FACIT-Fatigue scale scores through Week 24 and through Week 48. Time to confirmed improvement and time to confirmed deterioration in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (physical function, dyspnea, and fatigue), FACT-An Anemia, and FACIT-Fatigue scale scores from baseline through Week 24 and through Week 48. Mean changes in EORTC QLQ-C30 (physical function, dyspnea, and fatigue), FACT-An Anemia, and FACIT-Fatigue scale scores by visit through Week 48.
To describe the plasma concentration-time data to contribute to population pharmacokinetics and exposure-response analyses of elritercept.	Plasma concentration-time data for participants treated with elritercept.
To evaluate antidrug antibodies (ADA) in response to elritercept treatment.	Proportion of participants treated with elritercept reported to have ADA.
To compare time to progression to acute myeloid leukemia (AML) in participants treated with elritercept compared to epoetin alfa.	Time from randomization to first diagnosis of AML.
To assess overall survival of participants treated with elritercept versus epoetin alfa.	Time from randomization to the death of a participant from any cause.

1.1.2 Overall Design

Several key aspects of the trial design are summarized below.

Intervention Model:	Phase 3, randomized, 2-arm trial	Population Type:	Adult participants
Control:	Active control	Population Diagnosis or Condition:	Erythropoiesis-stimulating agent-naïve adults with anemia due to lower-risk myelodysplastic syndrome(s) who require RBC transfusions
Active Comparator:	Epoetin alfa	Population Age:	≥18 years
Trial Intervention Assignment Method:	Randomized 1:1 Stratification factors: • Ring sideroblasts (RS) positive (RS+) vs. RS negative (RS-) • Serum erythropoietin endogenous level as ≤200 U/L versus >200 U/L • 2-3 low transfusion burden versus 4-6 high transfusion burden pRBC units in 8 weeks preceding to randomization	Site Distribution:	Global

Number of Arms:

2.

Blinding:

Not applicable.

Number of Participants:

A minimum of 210 and up to 300 participants to be randomized 1:1 to receiving elritercept or epoetin alfa.

Arms and Duration:

Total duration of trial intervention for each participant:

A planned minimum of 24 weeks of trial intervention to demonstrate efficacy. The total duration of treatment will vary depending on the participant's response to treatment or toxicity or other reasons for discontinuation are met.

Total duration of trial participation for each participant:

Approximately 5 years from randomization.

CONFIDENTIAL

At the conclusion or termination of the trial or termination of a treatment arm in the trial, participants that continue to receive benefit may be given the opportunity for posttrial access to elritercept.

Arms and Duration Description:

Please refer to [Figure 1.a](#) for trial description.

Committees:

Data Monitoring Committee (DMC):

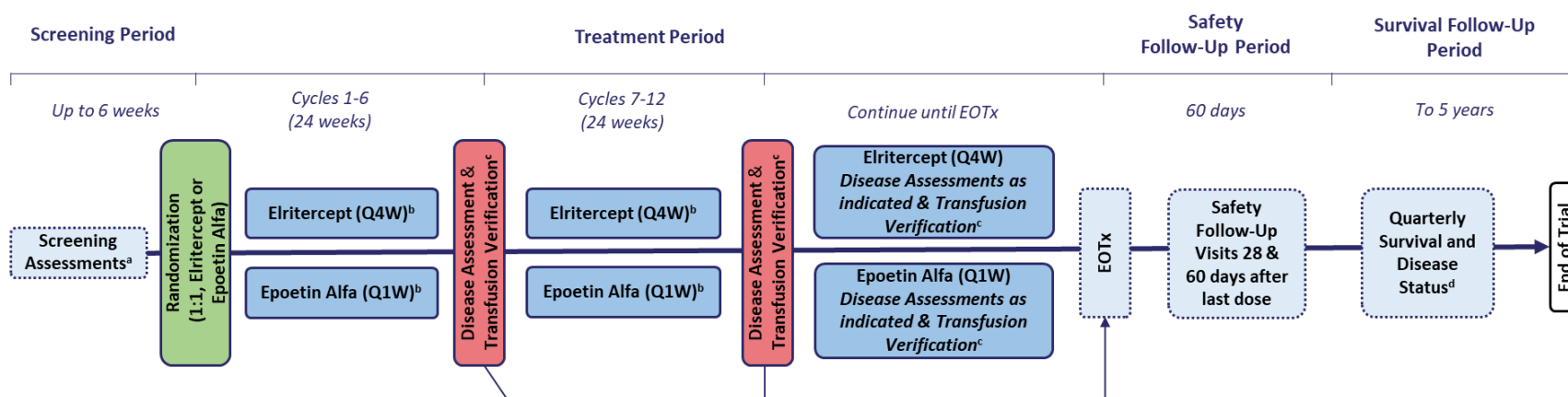
An external DMC will be formed and the voting members will be comprised of a minimum of 3 hematology-oncology medical experts not involved in this trial including one assigned as Chairperson, and an independent statistician not involved in this trial. The DMC Charter will define the roles and responsibilities of the members and sponsor, and the expectations for the data review meetings.

Steering Committee:

A Steering Committee will be formed and comprise of hematology-oncology medical experts in myelodysplastic syndrome who may or may not be involved in the trial. The Steering Committee Charter will define the responsibilities and expectations of the committee member and sponsor.

1.2 Trial Schema

Figure 1.a Trial Schema



AE: adverse event; AML: acute myeloid leukemia; C1D1: Cycle 1 Day 1; C3D1: Cycle 3 Day 1; EOTx: end of treatment; MDS: myelodysplastic syndrome(s); Q1W: once a week; Q4W: every 4 weeks; SFU: survival follow-up.

^a Screening assessments to be completed within 6 weeks prior to randomization, and may be extended by 2 weeks for a total of 8 weeks to complete transfusion history if needed and/or up to an additional 6 weeks for a total of 12 weeks for central pathology review of bone marrow for eligibility.

^b Elritercept and epoetin alfa to be administered in 28 day cycles. The starting dose will be used through C3D1 and up-titrated based on response criteria and safety/tolerability. Dose decrease may be required per protocol for an increase in hematology parameters or AEs. See Section 6.3

^c All participants complete collection of all RBC and platelet transfusions data after first dose until the next transfusion date after EOTx. If the participant had an EOTx visit before 24 weeks, continue to record transfusion data through 24 weeks; if no transfusions were reported between EOTx and 24 weeks, then monitor until the next transfusion date. Participants on treatment complete bone marrow collection for the MDS Disease Assessment at 24 and 48 weeks after C1D1.

^d Survival Follow-Up will assess survival status, determine the start and end dates of subsequent MDS treatments, date of progressive disease to AML (when applicable), and collect EQ-5D-5L for 5 years from randomization withdrawal from trial, whichever is earliest.

CONFIDENTIAL

1.3 Schedule of Activities

Table 1.c SoA (Treatment)

Treatment																						
			C1			C2		C3			C4			C5-6		C7		C8-12		C13+		
	Section	Screening ^a	D1	D8	D15	D1	D15	W9 D1	D8	D15	D1	D8	D15	D1	D15	W25 D1	D15	D1	D15	D1	D15	EOTx ^b
Visit Window (Days)		-42	0	±2	±3	±3	±3	±3	±2	±3	±3	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7
Informed Consent	10.3	X																				
Medical History	8.1.1.2	X																				
MDS Disease and Transfusion History	8.1.1.3 8.1.1.6	X ^{cd}																				
Coagulation panel ^e	8.1.1.7	X																				
HIV, HBV, HCV Status	5.4	X																				
Serum EPO ^e	8.3.4.2	X	X			X		X			X			X		X		X ^f		X ^f		X
Randomization	4.1.3		X ^g																			
Elritercept dosing ^h	6.3.1		X			X		X			X			X		X		X		X		
Epoetin Alfa dosing ⁱ	6.3.2		X (Dosing is weekly on every 7th day)																			
Safety Assessments																						
Weight	8.3.2.1		X			X		X			X			X		X		X		X		
Urinalysis ^e	8.3.4.2	X	X			X					X					X						X
Physical Exam and height (SCR	8.3.1	X	X			X		X			X			X		X		X		X		X

CONFIDENTIAL

Table 1.c SoA (Treatment)

Treatment																						
			C1			C2		C3			C4			C5-6		C7		C8-12		C13+		
	Section	Screening ^a	D1	D8	D15	D1	D15	W9 D1	D8	D15	D1	D8	D15	D1	D15	W25 D1	D15	D1	D15	D1	D15	EOTx ^b
Visit Window (Days)		-42	0	±2	±3	±3	±3	±3	±2	±3	±3	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7
only)																						
Vital Signs	8.3.2	X	X	X		X		X			X	X		X		X		X		X		X
Pregnancy Testing ^j	8.5	X	X _k			X		X			X			X		X		X		X		X
ECG	8.3.3.1	X		X								X										X
Echocardiogram _l	8.3.3.2	X														X				X		X
Hematology ^c	8.3.4.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry ^e	8.3.4.3	X	X	X		X		X			X	X		X		X		X		X		X
Adverse Events	8.4	X	X																			
Concomitant Medications	8.1.1.4	X	X																			
Concomitant Procedures	8.1.1.5	X	X																			
Disease Assessments																						
PB (for smears) and Bone Marrow	8.1 8.1.1.6 8.2.3 8.9.3	X ^d														X ^m				X ^m		X ^m
MDS Disease Assessment ⁿ	8.2.3															X				X		X
Transfusion Verification ^o	8.2.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^o
Biomarker Assessments																						

CONFIDENTIAL

Table 1.c SoA (Treatment)

Treatment																						
			C1			C2		C3			C4			C5-6		C7		C8-12		C13+		
	Section	Screening ^a	D1	D8	D15	D1	D15	W9 D1	D8	D15	D1	D8	D15	D1	D15	W25 D1	D15	D1	D15	D1	D15	EOTx ^b
Visit Window (Days)		-42	0	±2	±3	±3	±3	±3	±2	±3	±3	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7
ADA ^p	8.10		X		X	X		X			X	X		X		X		X		X		X
PK ^q	8.7		X	X	X	X		X	X ^q	X ^q	X	X		X		X		X		X		
Serum for circulating biomarkers (clinical) ^r	8.9.1		X			X		X			X			X		X		X		X		X
Serum for circulating biomarkers (exploratory) ^r	8.9.2		X	X	X	X	X	X			X					X		X ^f		X ^f		X
Blood for RNA (exploratory)	8.9.2		X	X	X	X	X	X														
Blood for MDS Mutations (exploratory) ^s	8.9.3		X																			
PRO Assessments and Resource Utilization																						
EORTC QLQ- C30 ^t	8.2.4.1	X	X			X		X			X			X		X		X		X		X
FACT-An Anemia scale ^t	8.2.4.2	X	X			X		X			X			X		X		X		X		X
PGI-S items ^t	8.2.4.5	X	X			X		X			X			X		X		X		X		X
EQ-5D-5L ^t	8.2.4.3		X			X		X			X			X		X		X		X		X
Transfusion Burden	8.2.4.4		X			X		X			X			X		X		X		X		X

CONFIDENTIAL

Table 1.c SoA (Treatment)

Treatment																						
			C1			C2		C3			C4			C5-6		C7		C8-12		C13+		
	Section	Screening ^a	D1	D8	D15	D1	D15	W9 D1	D8	D15	D1	D8	D15	D1	D15	W25 D1	D15	D1	D15	D1	D15	EOTx ^b
Visit Window (Days)		-42	0	±2	±3	±3	±3	±3	±2	±3	±3	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7
Assessment ^t																						
PGI-C items ^t	8.2.4.5					X		X			X			X		X		X		X		X
Healthcare Resource Utilization	8.11					X		X			X			X		X		X		X		X

Each cycle is 28 days, with visits on Day 1, and Days 8 and 15 as specified, and for epoetin alfa arm visit on Day 22 for dosing.

ADA: antidrug antibodies; C: cycle; D: day; ECG: electrocardiogram; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EOT: end of trial; EOTx: end of treatment; EPO: erythropoietin; FACT-An: Functional Assessment of Cancer Therapy-Anemia; MDS: myelodysplastic syndrome(s); NTBI: non-transferrin-bound iron; PB: peripheral blood; PGI-C: Patient Global Impression of Change; PGI-S: Patient Global Impression of Severity; PK: pharmacokinetics; POCBP: participant of childbearing potential; PRO: participant-reported outcome; RBC: red blood cell; SCR: screening; SOA: schedule of activities; TSAT: transferrin saturation; W: week.

^a **Screening** assessments to be completed within 6 weeks (42 days) prior to randomization, and may be extended by 2 weeks for a total of 8 weeks to complete transfusion history if needed and/or up to an additional 6 weeks for central pathology review of bone marrow for eligibility. See Section 5.6.2 for information on rescreening.

^b EOTx visit may occur no more than 7 days after the **decision** is made to discontinue trial intervention.

^c **Hematology** samples should be submitted to central laboratory. During screening, sample should be collected on the same date of bone marrow collection for disease classification but must be at least 14 days following an RBC transfusion and at least 7 days following a platelet transfusion (Refer to Section 8.1.1.6). Repeat sample collection ≤14 days prior to planned randomization, and, if applicable, post transfusion prior to randomization to confirm eligibility. During treatment, samples to be collected predose (≤2 days) on D1 and on D15 for central lab. For participants receiving epoetin alfa also report the predose (≤2 days) Hgb values for D8 and D22, local Hgb values are acceptable when dosing does not occur on site and not required if dosed at home. Additional hematology samples must be collected ≤3 days prior to any transfusion and as clinically indicated for safety evaluation. If samples are unable to be retrieved for central laboratory analysis, then local laboratory results must be collected and reported in the eCRFs. All available Hgb from the 8 weeks prior to planned randomization should be reported in the eCRF, to establish a baseline Hgb threshold.

CONFIDENTIAL

Table 1.c SoA (Treatment)

Treatment																						
			C1			C2		C3			C4			C5-6		C7		C8-12		C13+		
	Section	Screening ^a	D1	D8	D15	D1	D15	W9 D1	D8	D15	D1	D8	D15	D1	D15	W25 D1	D15	D1	D15	D1	D15	EOTx
Visit Window (Days)		-42	0	±2	±3	±3	±3	±3	±2	±3	±3	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7

^d **PB for blood smear and Bone marrow assessment for eligibility** includes bone marrow aspirate, bone marrow core biopsy, and PB. Samples should be submitted to central pathology laboratory approximately 28 days prior to planned randomization. Collections must be at least 14 days following an RBC transfusion and at least 7 days following a platelet transfusion (Refer to Section 8.1.1.6).

^e **Chemistry, coagulation, serum EPO, and urinalysis** samples should be submitted to central laboratory. During screening, all samples to be collected ≤14 days prior to planned randomization. Additional samples must be collected ≤3 days prior to any RBC transfusion for ferritin, TSAT, NTBI, and serum EPO. Additional samples may be collected as clinically indicated, and if samples are unable to be retrieved for central laboratory analysis, then local laboratory results should be collected and reported in the eCRFs. During treatment chemistry, serum EPO, and urinalysis samples should be collected predose.

^f To be taken quarterly starting on C10D1 (C13D1, C16D1, and so on)

^g The initiation of C1D1 trial intervention should occur no later than 3 days after randomization, but should occur on the same day as randomization whenever possible. Initiation of trial intervention may be extended beyond 3 days of randomization if approved by the medical monitor.

^h **Elritercept** therapy: Confirm Hgb ≤2 days pre-dose to confirm dosing. After 2 doses may up-titrate dose on or after C3D1 (Week 9).

ⁱ **Epoetin Alfa** therapy: Confirm Hgb ≤2 days pre-dose to confirm dosing; dosing is weekly on every 7th day, ±3 days for scheduling considerations. After 8 doses may up-titrate dose on or after C3D1 (Week 9).

^j Only applicable to POCBP. Pregnancy tests to be taken locally, not sent to a central laboratory.

^k **Pregnancy testing** during screening if negative and done <14 days prior to C1D1 dose does not need to be repeated on C1D1. Urine testing is sufficient unless positive test then beta human chorionic gonadotropin is required.

^l **Echocardiogram** required during screening if not done within 6 months prior to enrollment and every 6 months on trial intervention through safety follow-up.

^m **PB and Bone marrow assessment for on-trial disease assessment** visit windows are ±14 days. C7D1 (Week 25) bone marrow aspirate, bone marrow core biopsy, and PB are required. Collection of bone marrow aspirate and PB are required at C13D1 (Week 49) and EOTx if >6 months since prior collection. Report any additional bone marrow collections if clinically indicated as an unscheduled visit.

ⁿ Report MDS disease status at Week 25, Week 49 and every 6 months thereafter through EOTx. After Week 49 provide any bone marrow collections if clinically indicated per investigator discretion.

CONFIDENTIAL

Table 1.c SoA (Treatment)

Treatment																						
			C1			C2		C3			C4			C5-6		C7		C8-12		C13+		
	Section	Screening ^a	D1	D8	D15	D1	D15	W9 D1	D8	D15	D1	D8	D15	D1	D15	W25 D1	D15	D1	D15	D1	D15	EOTx
Visit Window (Days)		-42	0	±2	±3	±3	±3	±3	±2	±3	±3	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7

^a **Transfusion data** for RBC and platelet transfusions (see Section 8.2.1) must be collected after first dose until the next transfusion date after EOTx. If the participant had an EOTx visit before 24 weeks, continue to record transfusion data through 24 weeks; if no transfusions were reported between EOTx and 24 weeks, then monitor until the next transfusion date.

^b **ADA** sample should only be collected for the elritercept arm. Sample to be collected predose. Sample to be taken regardless of whether a dose is given. If a participant experiences a hypersensitivity reaction, injection site reaction, anaphylactic reaction, or other qualifying events at the discretion of the investigator, a sample for measurement of ADA will be collected as soon as possible after the reaction is noted. If a positive ADA is reported at the EOTx or Safety follow-up, then collect ADA samples quarterly for additional ADA testing until a negative result is obtained or until 12 months post-EOTx, whichever is earlier. Samples should optionally be collected at unscheduled visits for a participant who experiences an AE considered by the investigator to be consistent with hypersensitivity/infusion-related reaction.

^c **PK** sample should only be collected for the elritercept arm. Sample should be collected predose on dosing days. PK samples should be collected predose on D1, D8, D15 during the cycle when dose up-titration to 5.0 mg/kg and D1 of the subsequent cycle.

^d Serum sample **for circulating biomarkers** to be taken pre-dose. Serum will be collected to evaluate clinical parameters and exploratory biomarkers, See Table 8.e and Lab Manual for details. A decision to stop sample collection may take place at the sponsor's discretion.

^e Blood for MDS mutations to be taken predose on C1D1.

^f The **PRO** measures are to be administered on Day 1 of each cycle. A participant who discontinues treatment before C7D1 should return to the site to complete the PRO measures 4 weeks (± 7 days) from the date of their last dose and then every 4 weeks (± 7 days) thereafter until 24 weeks after their first dose. These visits can be consolidated with the EOTx visit, safety visits, or survival follow-up contacts if visit windows overlap, though the complete battery of PRO measures presented in Table 1.c (including the FACT-An Anemia scale) should be administered. The PRO measures are to be completed before any other assessments or trial procedures are performed (for example, before the participant sees the investigator, has any sample collections, receives transfusion, or is administered the trial intervention). The EORTC QLQ-C30 and Fact-An Anemia scale are to be administered during Screening at a visit that takes place ≥1 week before randomization.

CONFIDENTIAL

Table 1.d SoA (Follow-up)

	Section	Follow-up		
		Safety		Survival
		28 d Post Last Dose	60 d Post Last Dose	Quarterly From Last Dose
Visit Window (Days)		±7	+7	±14
Safety Assessments				
Urinalysis	8.3.4.3		X	
Physical Exam	8.3.1	X	X	
Vital Signs	8.3.2	X	X	
Pregnancy Testing ^a	8.5	X	X	
Hematology ^b	8.3.4.2	X	X	
Chemistry ^c	8.3.4.3	X	X	
AEs	8.4	X		
Concomitant Medications	8.1.1.4	X		
Concomitant Procedures	8.1.1.5	X		
Disease Assessments				
Survival and Disease Status	8.2.6.2			X ^d
Subsequent Treatment	8.2.6.2			X ^d
PRO Assessments				
EQ-5D-5L	8.2.4.3	X	X	X ^d
Biomarker Assessments				
ADA	8.10		X ^e	

ADA: antidrug antibodies; AE: adverse event; d: day; eCRF: electronic case report form; EOTx: end of treatment; MDS: myelodysplastic syndrome(s); POCBP: participant of childbearing potential; PRO: participant-reported outcome.

^a Only applicable to POCBP. Pregnancy tests to be taken locally, not sent to a central laboratory.

CONFIDENTIAL

Table 1.d SoA (Follow-up)

	Section	Follow-up		
		Safety		Survival
		28 d Post Last Dose	60 d Post Last Dose	Quarterly From Last Dose
Visit Window (Days)		±7	+7	±14

^b **Hematology** samples collected at visits to be submitted to central laboratory. Hematology samples collected ≤ 2 days prior to any transfusion and as clinically indicated for safety evaluation to be reported, and if samples are unable to be submitted to or if results are unavailable from central laboratory, then local laboratory results must be collected and reported in the eCRFs.

^c **Chemistry** samples collected at visits to be submitted to central laboratory. Any additional samples taken as clinically indicated for safety evaluation to be reported and if samples are unable to be retrieved for central laboratory, then local laboratory results must be reported in the eCRFs.

^d **Survival Follow-up:** Contact participant every 3 months (± 14 d) after date of EOTx to administer EQ-5D-5L by telephone and collect information on subsequent therapy for MDS. Report any progressive disease changes.

^e If a positive **ADA** is reported, then collect ADA samples quarterly for additional ADA testing until a negative result is obtained or until 12 months post-EOTx, whichever is earlier.

2.0 INTRODUCTION

2.1 Purpose of Trial

Elritercept, an investigational, modified activin receptor type IIA ligand trap designed to inhibit activin A and other select TGF- β superfamily ligands (activin B, GDFs 8, & 11), is being evaluated in diseases with ineffective hematopoiesis, including LR-MDS. This phase 3 registrational trial will evaluate the efficacy and safety of elritercept versus epoetin alfa in adult participants with transfusion-dependent anemia and ESA-naïve LR-MDS.

Refer to Section 1.2, Trial Schema and Section 1.3, SoA for more information about the trial design. Refer to Section 6.2 for introduction to elritercept.

2.2 Summary of Benefits and Risks

2.2.1 Benefit Summary

Cytopenias are common manifestations in patients with LR-MDS. Due to limited treatment options, there is a clear, unmet medical need in LR-MDS. Elritercept is designed to alter TGF- β signaling pathways at multiple stages of hematopoietic differentiation including RBC and platelet precursors.

In the phase 1, first-in-human trial, postmenopausal women treated with elritercept demonstrated increases in PD markers of hematopoiesis, such as reticulocytes, red blood cells, hemoglobin, and platelets in a dose-dependent fashion.

Preliminary efficacy results from the ongoing phase 2 trial, KER050-MD-201, demonstrate that elritercept treatment at the recommended dose may provide durable hematological benefits, including durable transfusion independence, in a broad population of patients with LR-MDS, including difficult-to-treat patients with HTB and/or RS- (Giagounidis et al. 2024).

Clinically meaningful improvements in quality-of-life measures observed in erythroid responders support broad potential for benefit in LR-MDS population. Fatigue burden (both experience and impact) was a primary driver of the observed improvements in QoL in transfusion independent responders versus nonresponders. Importantly, clinically meaningful improvements in fatigue scores were observed early and continued to improve over time in participants with more durable transfusion independent responses (Giagounidis et al. 2024).

Furthermore, preliminary PD results indicate potential for elritercept to improve multiple aspects of the underlying and systemic LR-MDS pathogenesis, including disruptions in iron homeostasis and bone metabolism, impaired hematopoiesis across multiple lineages, and increased cardiac strain, which collectively contribute to increased morbidity and mortality in patients with LR-MDS (Tan et al. 2024; Valcárcel et al. 2024).

Based on the results of these trials, elritercept has the potential to have clinically meaningful benefit in patients with LR-MDS.

2.2.2 Risk Summary and Mitigation Strategy

2.2.2.1 Trial Intervention

Safety and tolerability data from the phase 1 Trial KER-050-reported elritercept to be generally well tolerated and safety events did not appear to be dose dependent. Furthermore, elritercept has been well tolerated in participants with LR-MDS at doses up to 5.0 mg/kg (highest dose evaluated) in the ongoing phase 2 Trial KER050-MD-201 with no dose-limiting toxicities.

The most frequently reported TEAEs in participants with LR-MDS by MedDRA PT included diarrhoea, fatigue, dyspnoea, dizziness, anaemia, nausea, COVID-19, epistaxis and oedema peripheral.

Increases in hematological parameters (RBC, Hgb, reticulocytes, hematocrit, platelets) are expected pharmacological effects of elritercept treatment. Increases in blood pressure may occur alongside increases in Hgb values. Anti-hypertensive agents will be used to manage new-onset hypertension or exacerbations of preexisting hypertension. To minimize risks associated with increased hematological parameters, hypertension, and other AEs, dose-modification rules for individual participants, including dose delay and/or dose reduction, will be applied.

As with all biologics, there is potential for ADA with elritercept administration, which can be associated with increased drug clearance and hypersensitivity reactions. To minimize the risk, participants with medical history of allergy/anaphylaxis to elritercept or recombination proteins are excluded from the trial. Across trials with elritercept the reported incidence of ADA is low and does not appear to have any overt effects on serum elritercept exposure. In addition, observed injection-site reactions were reported infrequently and were localized, mild to moderate in severity, and manageable.

Elritercept has exhibited embryo-fetal and reproductive toxicity in nonclinical studies and, therefore, elritercept should not be administered to pregnant or nursing women. Precautions for male and female participants of childbearing potential are described in Section 5.4 and Appendix 13.1.

Safety of the participants will be monitored closely through AE reporting, clinical laboratory tests, vital signs, physical examinations, and ongoing review of unblinded data by an independent DMC (see Section 10.2.2).

Refer to the current elritercept IB for the most current information on the benefit-risk profile of elritercept. Include an assessment of known benefits and potential risks, including the basis of the risk (for example, preclinical studies or prior clinical trials).

2.2.2.2 Trial Procedures

This trial involves potential risks related to procedures, such as blood collection, transfusions, bone marrow aspirates and biopsies, and trial intervention injections. Blood collection may cause pain, bruising, bleeding, infection, or, in rare cases, dizziness or fainting. Injection site reactions can include redness, swelling, pain, or irritation. Bone marrow aspirates and biopsies may cause

localized pain and infrequently bleeding or infection, and, depending on the location, potential tissue or organ injury (see Section 8.9). The site-designated staff will carefully monitor participants, and any complications associated with these procedures should be managed according to local guidelines at the investigators' discretion.

2.2.2.3 Comparator Agent

Any potential adverse reactions associated with comparator, epoetin alfa, should be managed according to local guidelines and/or local label. Also see Section 6.9.2.

2.2.3 Overall Benefit:Risk Conclusion

In summary, elritercept demonstrates a favorable benefit-risk profile in the management of LR-MDS with transfusion-dependent anemia. Considering the manageable safety profile observed in elritercept trials and adherence to the treatment modification guidelines, the potential risks associated with elritercept treatment are outweighed by the anticipated benefits, including transfusion independence, improvement in anemia and thrombocytopenia, and QoL for participants with LR-MDS.

3.0 TRIAL OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1 Primary Objective + Associated Endpoint and Estimand

Table 3.a Primary Objective and Associated Endpoint

Primary Objective	Primary Endpoint
To evaluate the efficacy of elritercept on red blood cell transfusion independence (RBC-TI) for a minimum 12-week period within 24 weeks with concurrent mean hemoglobin (Hgb) increase ≥ 1.5 g/dL compared to epoetin alfa.	Proportion of participants who are RBC-TI for any consecutive ≥ 12 -week period from Cycle 1 Day 1 (C1D1) through Week 24 with concurrent mean Hgb increase ≥ 1.5 g/dL from baseline.

Primary Estimand

Table 3.b Estimand Framework for Primary Endpoint

Definition	The primary estimand is the treatment effect of elritercept compared to epoetin alfa on RBC-TI for a minimum 12-week period within 24 weeks from C1D1 with concurrent mean Hgb increase ≥ 1.5 g/dL compared to epoetin alfa.
Trial Intervention	Elritercept 3.75 mg/kg starting dose every 4 weeks (Q4W). Epoetin alfa 450 IU/kg starting dose once a week (Q1W).
Population	Adults with erythropoiesis-stimulating agent (ESA)-naïve lower-risk myelodysplastic syndrome(s) (LR-MDS).
Variable (or Endpoint)	RBC-TI for a minimum 12-week period within 24 weeks from C1D1 and concurrent Hgb increase ≥ 1.5 g/dL from baseline.
Strategy for Addressing Intercurrent Event	Intercurrent events (ICEs) mainly include treatment discontinuation prior to achieving the endpoint and protocol-prohibited medication usage (concomitantly or as subsequent treatment) prior to achieving the endpoint before the end of the 24-week period. Treatment policy strategy is used to handle the intercurrent event of treatment discontinuation prior to achieving the endpoint. Composite strategy is used to handle protocol-prohibited medication usage prior to achieving the endpoint. Strategy for handling missing data due to other ICEs, such as participant death or withdrawal of consent, is described in Section 9.2.3 Handling of Missing Data.
Population-Level Summary	Difference in proportion of participants to achieve RBC-TI for a minimum 12-week period within 24 weeks from C1D1 with concurrent mean Hgb increase ≥ 1.5 g/dL between elritercept and epoetin alfa arms.

3.2 Secondary Objectives + Associated Endpoints and Estimands

Table 3.c Secondary Objectives and Associated Endpoints

Secondary Objective	Secondary Endpoint
Key Secondary Objective: To compare the effect of elritercept on RBC-TI for a minimum 16-week period within 24 weeks versus epoetin alfa.	Key Secondary Endpoint: Proportion of participants who are RBC-TI for any consecutive ≥ 16 -week period from C1D1 through Week 24.
Key Secondary Objective: To compare effect of elritercept on RBC-TI for a minimum 12-week period within 24 weeks versus epoetin alfa.	Key Secondary Endpoint: Proportion of participants who are RBC-TI for any consecutive ≥ 12 -week period from C1D1 through Week 24.
Key Secondary Objective: To compare the effect of elritercept on RBC-TI for a minimum 24-week period within 24 weeks versus epoetin alfa.	Key Secondary Endpoint: Proportion of participants who are RBC-TI for a consecutive 24-week period from C1D1.
To compare the effect of elritercept versus epoetin alfa on favorable fatigue response with absence of RBC transfusion between the end of Week 12 and the end of Week 24.	Proportion of participants who have a confirmed meaningful improvement in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale score with no RBC transfusion between the end of Week 12 and the end of Week 24 among those with low baseline

CONFIDENTIAL

Table 3.c Secondary Objectives and Associated Endpoints

Secondary Objective	Secondary Endpoint
	scores or who maintain a high FACIT-Fatigue scale score with no meaningful deterioration and no RBC transfusion between the end of Week 12 and the end of Week 24 among those with high baseline scores.
To compare effect of elritercept on hematological improvement-erythroid (HI-E) for a minimum 8-week and for a minimum 12-week period within 24 weeks and within 48 weeks versus epoetin alfa.	Proportion of participants who achieved HI-E for a minimum 8-week and for a minimum 12-week period through Week 24 and Week 48.
To compare the effect of elritercept on RBC-TI at multiple time periods: for a minimum 8-week period within 24 weeks, and for a minimum 24-week period within 48 weeks versus epoetin alfa.	Proportion of participants who are RBC-TI for a minimum consecutive 8-week period from C1D1 through Week 24, and for a minimum consecutive 24-week period through Week 48.
To compare time to achieve RBC-TI for a minimum 12 weeks and a minimum 16 weeks RBC-TI within 24 weeks for participants receiving elritercept versus epoetin alfa	Time from date of first dose to first onset of achieving RBC-TI for minimum consecutive 12 weeks and for minimum consecutive 16 weeks through Week 24.
To compare the effect of elritercept on mean Hgb change through 24 and 48 weeks.	Mean Hgb change from baseline through Week 24 and through Week 48.
To compare duration of RBC-TI ≥ 12 weeks and ≥ 16 weeks RBC-TI achieved within 24 weeks for participants receiving elritercept versus epoetin alfa.	Maximum duration of RBC-TI for participants who achieved consecutive ≥ 12 weeks and ≥ 16 weeks of RBC-TI from C1D1 through Week 24.
To compare RBC transfusion burden during treatment for participants receiving elritercept versus epoetin alfa.	Total number and monthly average of packed red blood cells (pRBC) units received during treatment period.
To compare time to receive first RBC transfusion for participants receiving elritercept versus epoetin alfa.	Time from date of first dose to date of first RBC transfusion received during treatment period.
To compare time to achieve HI-E for a minimum ≥ 8 weeks within 24 weeks for participants receiving elritercept versus epoetin alfa.	Time from date of first dose to first onset of achieving HI-E for minimum consecutive 8 weeks through Week 24.
To compare the effect of elritercept versus epoetin alfa on health-related quality of life (HRQoL).	Proportion of participants with meaningful improvement in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (physical function, dyspnea, and fatigue), Functional Assessment of Cancer Therapy-Anemia (FACT-An), and FACIT-Fatigue scale scores through Week 24 and through Week 48. Time to confirmed improvement and time to confirmed deterioration in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (physical function, dyspnea, and fatigue), FACT-An Anemia, and FACIT-Fatigue scale scores from baseline through Week 24 and through Week 48. Mean changes in EORTC QLQ-C30 (physical function,

CONFIDENTIAL

Table 3.c Secondary Objectives and Associated Endpoints

Secondary Objective	Secondary Endpoint
	dyspnea and fatigue), FACT-An Anemia, and FACIT-Fatigue scale scores by visit through Week 48.
To describe the plasma concentration-time data to contribute to population pharmacokinetics and exposure-response analyses of elritercept.	Plasma concentration time data for participants treated with elritercept.
To evaluate antidrug antibodies (ADA) in response to elritercept treatment.	Proportion of participants treated with elritercept reported to have ADA.
To compare time to progression to acute myeloid leukemia (AML) in participants treated with elritercept compared to epoetin alfa.	Time from randomization to first diagnosis of AML.
To assess overall survival of participants treated with elritercept versus epoetin alfa.	Time from randomization to the death of a participant from any cause.

Secondary Estimands

Table 3.d Estimand Framework for Alpha Controlled Secondary Endpoints

Definition	Key secondary estimand 1 is the effect of elritercept on RBC-TI for a minimum 16-week period within 24 weeks versus epoetin alfa.
Trial Intervention	Elritercept 3.75 mg/kg starting dose Q4W. Epoetin alfa 450 IU/kg starting dose Q1W.
Population	Adults with ESA-naïve LR-MDS.
Variable (or Endpoint)	RBC-TI for any consecutive ≥ 16 -week period from C1D1 through Week 24.
Strategy for Addressing Intercurrent Event	ICEs and ICEs handling strategies are the same as for the primary endpoint.
Population-Level Summary	Difference in proportion of participants to achieve RBC-TI for a minimum 16-week period within 24 weeks between elritercept and epoetin alfa arms.
Definition	Key secondary estimand 2 is effect of elritercept on RBC-TI for a minimum 12-week period within 24 weeks versus epoetin alfa.
Trial Intervention	Elritercept 3.75 mg/kg starting dose Q4W. Epoetin alfa 450 IU/kg starting dose Q1W.
Population	Adults with ESA-naïve LR-MDS.
Variable (or Endpoint)	RBC-TI for any consecutive ≥ 12 -week period from C1D1 through Week 24.
Strategy for Addressing Intercurrent Event	ICEs and ICEs handling strategies are the same as for the primary endpoint.

CONFIDENTIAL

Table 3.d Estimand Framework for Alpha Controlled Secondary Endpoints

Population-Level Summary	Difference in proportion of participants to achieve RBC-TI for a minimum 12-week period within 24 weeks between elritercept and epoetin alfa arms.
Definition	Key secondary estimand 3 is the effect of elritercept on RBC-TI for a minimum 24-week period within 24 weeks versus epoetin alfa.
Trial Intervention	Elritercept 3.75 mg/kg starting dose Q4W. Epoetin alfa 450 IU/kg starting dose Q1W.
Population	Adults with ESA-naïve LR-MDS.
Variable (or Endpoint)	RBC-TI for a consecutive 24-week period from C1D1 through Week 24.
Strategy for Addressing Intercurrent Event	ICEs and ICEs handling strategies are the same as for the primary endpoint.
Population-Level Summary	Difference in proportion of participants to achieve RBC-TI for a consecutive 24-week period within 24 weeks between elritercept and epoetin alfa arms.
Definition	Estimand for additional alpha-controlled secondary endpoint is the effect of elritercept on favorable fatigue response with absence of RBC transfusion between the end of Week 12 and the end of Week 24.
Trial Intervention	Elritercept 3.75 mg/kg starting dose Q4W. Epoetin alfa 450 IU/kg starting dose Q1W.
Population	Adults with ESA-naïve LR-MDS.
Variable (or Endpoint)	Proportion of participants who have a confirmed meaningful improvement in FACIT-Fatigue scale score with no RBC transfusion between the end of Week 12 and the end of Week 24 among those with low baseline scores or who maintain a high FACIT-Fatigue scale score with no meaningful deterioration and no RBC transfusion between the end of Week 12 and the end of Week 24 among those with high baseline scores.
Strategy for Addressing Intercurrent Event	ICEs mainly include treatment discontinuation prior to response and protocol-prohibited medication use (<u>concomitantly or as subsequent treatment</u>) prior to achieving the endpoint before the end of the 24-week period. Treatment policy strategy is used to handle the ICEs of treatment discontinuation prior to achieving the endpoint between the end of Week 12 and the end of Week 24. Composite strategy is used to handle protocol-prohibited medication usage prior to achieving the endpoint. Strategy for handling missing data due to other ICEs, such as participant death or withdrawal of consent, is described in Section 9.2.3 Handling of Missing Data.
Population-Level Summary	Difference in proportion of participants who achieve favorable fatigue response between the end of Week 12 and the end of Week 24 between elritercept and epoetin alfa arms.

3.3 Safety Objective + Associated Endpoint

Table 3.e Safety Objective and Associated Endpoint

Safety Objective	Safety Endpoint
To evaluate the safety of elritercept versus epoetin alfa.	Frequency, severity, and relationship of treatment-emergent adverse events and serious adverse events reported in participants treated with elritercept versus epoetin alfa; and change in baseline clinical laboratory values, vital signs, echocardiograms, and electrocardiograms in participants treated with elritercept versus epoetin alfa.

Safety Estimands

Not applicable.

3.4 Exploratory Objectives + Associated Endpoints

Table 3.f Exploratory Objectives and Associated Endpoints

Exploratory Objective	Exploratory Endpoint
To assess the effect of elritercept on neutrophil counts within 24 weeks versus epoetin alfa.	Mean change from baseline in absolute neutrophil count Day 1 through 24 weeks; and, Proportion of participants achieving mean absolute increase in neutrophil counts of $\geq 0.5 \times 10^9/L$ for consecutive ≥ 8 weeks through Week 24.
To assess the effect of elritercept on thrombopoiesis and platelet parameters through Week 24 and Week 48 versus epoetin alfa.	Mean change from baseline in platelet count through 24 and 48 weeks; and, Proportion of participants achieving mean absolute increase in platelet counts of $\geq 30 \times 10^9/L$ consecutive ≥ 8 weeks through 24 weeks and 48 weeks.
To assess the effect of elritercept on erythropoiesis and other clinical biomarkers through Week 24 and Week 48 versus epoetin alfa.	Mean change from baseline in biomarkers of erythropoiesis and other clinical biomarkers through 24 weeks and 48 weeks.
To assess the effect of elritercept on iron overload and homeostasis through Week 24 and Week 48 versus epoetin alfa.	Mean change from baseline by visit in serum ferritin levels through Week 24 and Week 48.
To assess the effect of elritercept on clinical biomarkers for osteoblast activity through Week 24 and Week 48 versus epoetin alfa.	Mean change from baseline bone specific alkaline phosphatase may be assessed.
To evaluate mutations from baseline and on-treatment bone marrow samples.	Correlation of baseline mutations (for example, SF3B1) with pharmacodynamic and efficacy readouts; and, Evaluate changes from baseline variant allele frequency for select molecular variants with

Table 3.f Exploratory Objectives and Associated Endpoints

Exploratory Objective	Exploratory Endpoint
	significance in myelodysplastic syndromes.
To evaluate exploratory circulating biomarkers.	Evaluate and compare treatment effects on downstream biological pathways based on circulating biomarker profiles, including, but not limited to, cytokines and growth factors.
To evaluate RNA transcripts in blood samples for elritercept versus epoetin alfa.	Evaluate and compare treatment effects on downstream biological pathways based on transcriptomic profiles.
To assess the effect of elritercept on healthcare resource utilization versus epoetin alfa.	Evaluate the healthcare resource utilization outcomes associated with trial intervention from Cycle 2 Day 1 through end of treatment.
To assess the effect of elritercept on HRQoL versus epoetin alfa.	Mean changes in EORTC QLQ-C30 scale scores (other than physical function, dyspnea, and fatigue), EQ-5D-5L utility index and visual analog scale scores, transfusion burden assessment score, and Patient Global Impression of Severity scores as well as mean Patient Global Impression of Change scores by visit through Week 48.
To assess the effect of elritercept on transfusion reliance versus epoetin alfa	Mean Time Without Transfusion Reliance (TWiTR) and quality-adjusted TWiTR (Q-TWiTR) through Week 24 and through Week 48.
To evaluate hematopoietic precursors and bone marrow (BM) cellularity in BM for elritercept versus epoetin alfa.	Evaluate and compare treatment effects on erythroid, granulocytic, megakaryocytic precursors; and evaluate and compare normalization of BM cellularity.
To evaluate response with Molecular International Prognostic Scoring System (IPSS-M) classification.	Categorization by IPSS-M classification at baseline and later timepoints and compare to response.
To evaluate reduction in pRBC units $\geq 50\%$ for ≥ 12 and ≥ 24 weeks.	Proportion of participants who achieved reduction in pRBC units $\geq 50\%$ for ≥ 12 weeks from C1D1 through end of trial (EOT). Proportion of participants who achieved reduction in pRBC units $\geq 50\%$ for ≥ 24 weeks from C1D1 through EOT.
To evaluate duration of reduction in pRBC units $\geq 50\%$ for ≥ 12 and ≥ 24 weeks.	Duration of reduction in pRBC units $\geq 50\%$ for participants who achieved reduction in pRBC units $\geq 50\%$ for ≥ 12 weeks from C1D1 through EOT. Duration of reduction in pRBC units $\geq 50\%$ for participants who achieved reduction in pRBC units $\geq 50\%$ for ≥ 24 weeks from C1D1 through EOT.

Exploratory Estimands

Not applicable.

CONFIDENTIAL

4.0 TRIAL DESIGN

4.1 Description of Trial Design

4.1.1 Intervention Model

This is a registrational, phase 3, multicenter, randomized, open-label, active-controlled, parallel-arm, interventional trial to evaluate the efficacy and safety of elritercept versus epoetin alfa for treatment of transfusion-dependent anemia in ESA-naïve adult participants with very low-, low-, or intermediate-risk MDS (LR-MDS according to classification by 2012 IPSS-R).

The design of this randomized trial includes prospective stratification based on baseline EPO level, transfusion burden, and RS status. It features an active-control arm and parallel-arm design to minimize potential bias in the assignment of the trial intervention or in data interpretation. Furthermore, the multicenter nature of the trial conducted across various countries will provide assurance that the results are likely to have universal applicability.

To avoid bias and ensure comparability across arms, accurate and consistent disease-associated transfusions will be collected during the 8 weeks of pretrial period for determination of transfusion burden at baseline. Of note, RBC transfusion burden will include only transfusions with a pretransfusion Hgb <9 g/dL. This pretransfusion Hgb limit will be applied during the treatment period when considering administration of RBC transfusions.

Approximately, from 210 to 300 participants will be enrolled in this trial from approximately 150 trial sites globally. A participant is considered to be enrolled in the trial once the ICF has been signed and the participant has been randomized.

This trial is designed as a superiority trial which includes:

- IA for futility and sample size re-estimation when approximately 110 randomized participants have completed 24 weeks of treatment or discontinued before reaching 24 weeks of treatment.
- Primary Analysis for superiority when all randomized participants have completed 24 weeks of treatment or discontinued treatment before reaching 24 weeks.

4.1.2 Trial Duration

The expected total duration of the trial is approximately 8 years. This includes approximately 3 years of enrollment, and 5 years from last randomized participant.

The duration of participation for a participant will be approximately 5 years from randomization. The trial will consist of the following phases:

- Screening period: Up to 42 days prior to randomization, but it may be extended to confirm eligibility (For details see [Table 1.c](#)).
- Treatment period: At least 24 weeks. After 24 weeks, an MDS Disease Assessment will be conducted, and treatment may continue until discontinuation per protocol (Section [7.1](#)).

CONFIDENTIAL

- Posttreatment follow-up period: At least 5 years from the date of the first dose of trial intervention.

Participants will be followed until lost to follow-up, consent withdrawal, death, or trial termination, whichever occurs first.

Participants who proceed to alternative therapy will be discontinued from trial intervention. All participants who discontinue trial intervention will be followed for subsequent treatments, disease progression status, and survival as specified in the SoA (Section 1.3).

4.1.3 Method of Assignment to Trial Intervention

The treatment assignment (stratified randomization for baseline EPO level, transfusion burden, and RS status) will occur once all required screening procedures have been completed and all inclusion and exclusion criteria have been assessed to determine eligibility of the potential participant. Participants deemed eligible for the trial will be randomized 1:1 to either elritercept or epoetin alfa by a central randomization procedure using IRT.

4.1.4 Additional Description of Design

Not applicable.

4.1.5 Participant Input Into Design

Participant input was not sought on the design of the trial.

4.2 Rationale for Trial Design

4.2.1 Rationale for Intervention Model

This is a registrational, phase 3, multicenter, randomized, open-label, active-controlled, parallel-arm, interventional trial to evaluate the efficacy and safety of elritercept versus epoetin alfa for treatment of transfusion-dependent anemia in ESA-naïve adult participants with very low-, low-, or intermediate-risk MDS (LR-MDS according to classification by 2012 IPSS-R).

The trial is randomized 1:1 to offer the most efficiency in sample size, reduce selection bias, and improve trial integrity. The open-label design is the least burdensome approach for participants and for ethical considerations given there is a difference in treatment schedules for monthly elritercept (Q4W) compared to weekly epoetin alfa. A stratified randomization scheme is used to control heterogeneity and to balance key factors known to affect efficacy, which may impact trial endpoint assessment across the 2 treatment arms.

Epoetin alfa was chosen as the comparator as a universally accepted standard of care for first line LR-MDS without del(5q) mutation, including participants with RS- LR-MDS. This phase 3 trial is designed to provide evidence to support the regulatory approval of elritercept for the treatment of anemia in adults with very low-, low-, or intermediate-risk MDS.

4.2.2 Rationale for Duration

The primary and key secondary objectives of this phase 3 trial require a minimum 24 weeks of treatment for assessment of response and continued treatment until clinical benefit is no longer observed is consistent with current treatment guidelines including the IWG 2018. The treatment period duration is adequate to provide sufficient data for trial endpoints including efficacy, PROs, and PK.

The safety follow-up period for at least 60 days after EOTx is consistent with the required observation of AEs through $5 \times$ half-lives of the trial intervention and sufficient to identify any ADA events.

The survival follow-up period of 5 years from randomization is adequate to report potential progression to higher-risk MDS (Higher-risk MDS; HR-MDS per IPSS-R), myeloproliferation (for example, clinically significant increases in blasts), or AML given the literature reported time to event data, as well as adequate time to report survival trends in this typically elderly population.

4.2.3 Rationale for Endpoints

These primary and secondary endpoints reflect the goal of therapy to reduce transfusion requirements or achieve transfusion independence, as well as to improve peripheral blood values (that is, increasing Hgb levels).

4.2.3.1 Rationale for Disease and Hematologic Response Assessment Endpoints

Therapy goals for this population include alleviating symptoms of anemia, decreasing transfusion dependency or inducing transfusion independence, and improving QoL. The primary endpoint of RBC-TI is defined as the proportion of participants who are RBC transfusion-free for any consecutive 12-week period during the first 24-week period of trial intervention associated with a concurrent mean Hgb increase ≥ 1.5 g/dL compared to baseline. This endpoint is based on modified IWG 2006 recommendations, which define response criteria as the absence of transfusions for at least 8 weeks. Using a longer duration of transfusion independence ≥ 12 weeks and including a concurrent ≥ 12 weeks mean Hgb increase of ≥ 1.5 g/dL compared to baseline will increase the clinical meaningfulness of the endpoint. This response assessment of transfusion independence for at least 12 weeks, along with concurrent Hgb improvement, supports achieving a response that exceeds the response definition that is minimally accepted by the guidelines, including IWG 2006.

Anemia is an established negative prognostic factor in MDS. Male and female patients with Hgb levels lower than 9 and 8 g/dL, respectively, were found to be at higher risk of morbidity and mortality, mainly due to an increased risk of cardiac complications ([Malcovati et al. 2006](#)). Furthermore, progressive anemia and the need for regular transfusions are associated with significant declines in QoL, especially among older patients with MDS ([Cheson et al. 2006](#)). Lower Hgb levels often lead to increased fatigue and decreased physical functioning, further

complicating the management of MDS and negatively affecting the overall well-being of the patient.

Given the severe impact of anemia on both prognosis and QoL, managing Hgb levels in MDS patients is crucial. An Hgb increase of at least 1.5 g/dL would be a clinically relevant effect on erythropoiesis and improvement of anemia ([Cheson et al. 2006](#)). Anemia may improve with frequent RBC transfusions. However, these transfusions can lead to significant clinical complications, including transfusion reactions, infections, and iron overload. In patients with MDS, dependence on RBC transfusion adversely affects the likelihood of survival. It is believed that the detrimental effect of transfusion dependence on outcomes in patients with MDS stems from more severe bone marrow insufficiency linked to transfusion dependence and, possibly, iron overload. Additionally, transfusion dependence has a significant impact on physical, functional, and social well-being and plays an independent and major role in the deterioration of HRQoL ([Germing et al. 2019](#)).

Overall, patients with MDS who experience chronic cytopenias and hematologic improvement leading to transfusion independence represent a clinically significant treatment objective ([Balducci 2006](#)). Therefore, transfusion independence is a critical marker of treatment success in lower-risk MDS due to the impact of anemia on QoL and overall health outcomes ([Platzbecker et al. 2024](#)).

Therefore, in this trial, a prolonged period of 12 weeks of transfusion independence and a mean Hgb increase of at least 1.5 g/dL illustrates a significant direct clinical benefit and would be considered clinically relevant.

4.2.3.2 *Rationale for Secondary Endpoints and Additional Analyses*

Secondary endpoints include endpoints evaluating efficacy (RBC-TI for 12 weeks, 16 weeks, and 24 weeks over the first 24-week period of trial intervention), which reflect clinically relevant goals of therapy for lower-risk MDS patients. Considering the population (LTB and HTB) enrolled in this trial, it would be reasonable to regard these efficacy endpoints as clinically meaningful, as IWG recommendations recognize the significant clinical benefit of extended transfusion independence. In addition, a key secondary endpoint was included to evaluate HI-E response (≥ 8 weeks) as per IWG 2006 (see Section [17.2](#)).

The evaluation of PROs is an increasingly important aspect of clinical efficacy in lower-risk MDS trials. Such data provide an understanding of the impact of treatment on symptomatic anemia from the participants perspective and offer insights into participant experience that may not be captured through physician reporting.

4.2.3.3 *Exploratory Endpoint on Molecular Mutations including SF3B1*

Recurrent mutation of the SF3B1 gene was found in 20% of patients with MDS. Notably, these mutations were found in 65% of patients whose disease was characterized by the presence of RS ([Papaemmanuil et al. 2011](#)).

Furthermore, analysis of SF3B1 mutations has revealed remarkable insights into their prognostic value in MDS. The presence of SF3B1 mutations not only correlates with specific disease phenotypes, such as RS, but also serves as an independent predictor of favorable clinical outcomes. Patients with SF3B1 mutations exhibit better overall survival and a lower risk of progression to AML. These findings underscore the importance of molecular profiling in enhancing the classification, prognosis, and therapeutic strategies for MDS patients (Malcovati et al. 2013).

This trial aims to further evaluate the prognostic value of specific MDS-related gene mutations, including SF3B1, within the trial population. Additionally, we may investigate the clinical benefits associated with these gene mutations, particularly in relation to treatment responses to elritercept. This may involve a detailed analysis of patient outcomes, including transfusion independence and Hgb levels, to determine how SF3B1 and other relevant genetic mutations influence therapeutic efficacy.

4.2.4 Rationale for IA

One IA is planned after approximately 110 participants have completed 24 weeks of treatment or discontinued treatment before reaching 24 weeks. This IA is for futility and sample size re-estimation. No statistical significance claim will be made for any endpoint at the IA; therefore, no alpha will be allocated.

4.2.5 Rationale for Comparator

In LR-MDS, frontline treatment aims to alleviate anemia, reduce transfusion burden, and improve QoL (Platzbecker 2019). Globally, current available treatment options include supportive care with RBC transfusions, ESAs such as epoetin-alfa, and in some countries, luspatercept. ESAs have been used for many years to treat anemia in patients with lower-risk MDS. The use of ESAs is recommended by international clinical practice guidelines, due to the large body of evidence demonstrating their effectiveness in lower-risk MDS (Gascón et al. 2019). In a phase 3, randomized trial, ESA (epoetin alfa) improved erythroid responses (increased Hgb) compared to placebo (31.8% versus 4.4%, $p < 0.001$) (Fenaux et al. 2018).

Considering the international guidelines/recommendations, approval and access in many countries, epoetin alfa was selected as the active comparator to ensure that all participants in the trial have the opportunity to receive the standard of care first-line therapy for the treatment of anemia in lower-risk MDS patients, or to receive the investigational agent (Fenaux et al. 2020; Malcovati et al. 2013).

4.2.6 Rationale for Adaptive or Novel Trial Design

The trial is based on an adaptive design with sample size re-estimated at the IA. This adaptive design approach is chosen to mitigate the uncertainty of the treatment effect size of elritercept over epoetin alfa. The adaptive design helps to make the trial more efficient by re-estimating the sample size that is needed to target statistical power for the primary analysis based on the

observed effect size at the IA, while maintaining its integrity. It also serves as a futility analysis to potentially minimize exposing participants to ineffective treatment by adapting based on early evidence.

4.2.7 Other Trial Design Considerations

This trial will collect the race and ethnicity parameters specified in Section 8.1.1.1. Race and ethnicity data are collected in this trial to understand how similar the trial population is to the population with LR-MDS at large and to help researchers understand if the efficacy and/or safety of elritercept could be different for people of different races or ethnicities.

4.2.8 Rationale for Stratification

The randomization is stratified by transfusion burden, RS status, and endogenous sEPO levels. This approach will help balance potential prognostic differences between treatment arms and provide a more accurate assessment of the treatments' effect on efficacy and safety.

4.2.8.1 RBC Transfusion Burden at Baseline

In this trial, RBC transfusion burden is considered an important stratification factor due to the likelihood of transfusion independence being correlated with the degree of transfusion burden at time of enrollment. To ensure balance between treatment arms, participants will be stratified by LTB and HTB.

- Participants who receive 2 to 3 pRBC units during the 8-week period immediately prior to randomization will be identified as LTB stratification factor.
- Participants who receive 4 to 6 pRBC units during the 8-week period immediately prior to randomization will be identified as HTB stratification factor.

4.2.8.2 RS Status at Baseline

The trial population will include participants identified at screening to have RS+ or RS- status. Randomization will be stratified by RS status to balance the distribution of RS+ and RS- participants between the 2 treatment arms, thereby addressing any associated potential prognostic differences between the 2 arms. Furthermore, RS status stratification will reduce the variability and enhance the reliability of the trial outcomes reported.

Participants will be identified as RS+ or RS- as reported by the central laboratory independent reviewer prior to randomization. RS+ is defined as RS $\geq 15\%$ of erythroid precursors in bone marrow or $\geq 5\%$ if SF3B1 mutation is present.

4.2.8.3 Endogenous sEPO Level at Baseline

This trial will enroll participants with endogenous sEPO levels less than 500 U/L at screening. Literature reports clinically meaningful differences with epoetin alfa in response rates for

transfusion independence and Hgb improvement with levels reported at or less than 200U/L (Fenaux et al. 2018).

Stratification for endogenous sEPO level ≤ 200 U/L and >200 U/L at screening will be balanced between treatment arms to reduce the impact of endogenous sEPO levels on the trial endpoints and will allow more accurate assessment of the effect of the 2 treatment arms. Participants sEPO level should be identified from central laboratory during screening.

4.3 Access to Trial Intervention After EOT

4.3.1 Posttrial Access

At the conclusion or termination of the trial or termination of a treatment arm in the trial, participants may be given the opportunity to enroll in a separate open-label rollover trial, a single patient IND, or other regulated access to continue receiving elritercept if they have, in the opinion of the investigator and confirmed by the sponsor, experienced a clinically important benefit from elritercept that they received in the trial, have no alternative therapeutic option, and would be harmed without continued access. Such a protocol would be developed for the elritercept clinical development program to ensure availability of posttrial access to elritercept across multiple studies.

4.3.2 Duration of Posttrial Access

Continued access to elritercept for participants will be terminated for those individuals who are no longer receiving clinical benefit from elritercept, the benefit-risk no longer favors the individual, if elritercept becomes available either commercially or via another access mechanism, or when an alternative appropriate therapy becomes available. Posttrial access may be terminated in a country or geographical region where marketing authorization has been rejected, the development of elritercept has been suspended or stopped by the sponsor, or elritercept can no longer be supplied.

4.4 Start of Trial and EOT

4.4.1 Start of Trial Definition

The start date of the trial is defined as the date the first participant has signed ICF at any site globally. For clinical trial disclosure purposes, trial start date will be the date the first participant is consented at any site globally.

4.4.2 Other Key Trial Timepoints

An IA will be conducted after approximately 110 participants have completed 24 weeks of treatment or discontinued before reaching 24 weeks of treatment.

The primary analysis will be conducted after all randomized participants have completed or had the opportunity to receive 24 weeks of treatment or discontinued before reaching 24 weeks.

The secondary analysis will be conducted after all randomized participants have completed 48 weeks of treatment or discontinued before reaching 48 weeks.

The final analysis of disease progression and overall survival will be conducted 5 years after randomization of the last participant.

4.4.3 Early Trial or Site Closure

The sponsor may suspend or terminate part of the trial, or the trial in its entirety, at any time for any reason. The sponsor reserves the right to close a trial site at its sole discretion. Sites will be closed upon trial completion.

Sites may be closed by the sponsor due to the investigator's failure to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines; inadequate or no recruitment (evaluated after a reasonable amount of time); inclusion of the total number of participants earlier than expected, or other reasons not listed herein.

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

A trial site is considered closed when all required documents and trial supplies have been collected, and a trial-site closure visit has been performed.

Please see Section 10.5, Early Site Closure or Trial Termination, for criteria and responsibilities related to early site closure or trial termination.

4.4.4 EOT Definition

The trial completion date is defined as the date on which the last participant completes the final protocol-defined assessment(s). This includes the follow-up visit or contact (in person and/or by phone or video), whichever is later (refer to Section 1.3 for the defined follow-up period for this protocol). The latest date for trial completion will be the date on which all participants enrolled in the trial have had the opportunity for treatment or survival follow-up through 5 years after randomization of the last participant and completes the final protocol-defined assessment(s) for the associated visits, or have withdrawn consent, are declared lost to follow-up, have died, or until trial closure, whichever is earliest (refer to Section 1.3 for the defined follow-up period for this protocol).

5.0 TRIAL POPULATION

5.1 Selection of Trial Population

Adult participants (≥ 18 years) with anemia due to very low-, low-, or intermediate-risk MDS classification according to 2012 IPSS-R, with a bone marrow blast count of $< 5\%$ and without del(5q) mutation (Arber et al. 2016; Greenberg et al. 2012), who are ESA-naïve and require RBC transfusions. Diagnosis of LR-MDS will be confirmed by an independent central reader during

the screening period using WHO 2016 ([Arber et al. 2016](#)) and IPSS-R ([Greenberg et al. 2012](#)) criteria.

A participant is considered enrolled in the trial once the ICF is signed, and the participant has been randomized.

5.2 Rationale for Trial Population

In the US in 2024, the incidence of MDS ranged from 3.2 to 4.6 per 100,000 persons-years, increasing to 40.8 per 100,000 person-years in those aged ≥ 70 years. The estimated prevalence was 17.6 per 100,000 persons (Leukemia and Lymphoma Society. Facts and Statistics Overview. Leukemia and Lymphoma Society 2024. [lls.org/facts-and-statistics/facts-and-statistics-overview/#Myelodysplastic%20Syndromes%20\(MDS\)](https://lls.org/facts-and-statistics/facts-and-statistics-overview/#Myelodysplastic%20Syndromes%20(MDS))). Accessed on April 4, 2025, American Cancer Society. Key Statistics for MDS. Atlanta. American Cancer Society; 2024. cancer.org/cancer/types/myelodysplastic-syndrome/about/key-statistics.html. Accessed on April 4, 2025). Among MDS patients, two-thirds are diagnosed with LR-MDS, defined as very low-, low-, or intermediate-risk according to the IPSS-R ([Greenberg et al. 2012](#)). The median overall survival for LR-MDS ranges from 2.3 to 8.8 years ([Gangat et al. 2016](#); [Greenberg et al. 2012](#); [Mądry et al. 2023](#)).

WHO 2016 and IPSS-R are appropriate for eligibility determination as these are well-established, validated systems used across several MDS studies and in worldwide clinical practice. While recent updates to WHO criteria (WHO 5th Edition) ([Khoury et al. 2022](#)) and IPSS prognostic categorizations (IPSS-M) ([Bernard et al. 2022](#)) represent important developments in the field, current understanding of MDS is largely rooted in analyses using WHO 2016 and IPSS-R.

Anemia is the most common cytopenia of LR-MDS patients ([de Swart et al. 2015](#); [Nachtkamp et al. 2016](#)) and is associated with a significantly increased risk of cardiac disease and shorter overall survival ([Greenberg et al. 2012](#); [Malcovati et al. 2011](#)). Severe anemia can manifest in multiple symptoms, including weakness, fatigue, and shortness of breath, partly due to cardiovascular implications ([Oliva et al. 2011b](#)). Most patients with anemia require regular RBC transfusions ([Platzbecker 2020](#)), with 51% becoming transfusion dependent ([de Swart et al. 2015](#)). Transfusion dependence substantially impacts physical, functional, and social well-being, placing significant burden on patients, caregivers, and the healthcare system ([de Swart et al. 2020](#); [Lewis et al. 2024](#); [Lucioni et al. 2013](#); [Platzbecker et al. 2012](#)). Additionally, frequent transfusions, coupled with impaired iron utilization from ineffective hematopoiesis, often lead to iron overload, which can damage vital organs and exacerbate morbidity and mortality risks among LR-MDS patients ([Gattermann 2018](#); [Jouzier et al. 2022](#)). Compared to transfusion dependent patients, the risk of death was 59% lower for transfusion independent patients ([Harnan et al. 2016](#)).

This trial population includes adult participants diagnosed with IPSS-R LR-MDS without the del(5q) mutation. The trial is designed to evaluate first-line therapy enrolling participants with a sEPO level of less than 500 U/L who are ESA-naïve and transfusion dependent. Transfusion

dependency is defined as requiring between 2 to 6 pRBC units during the 8 weeks preceding randomization. Supportive care with RBC transfusion and ESAs, such as epoetin alfa, are current treatment options for patients with LR-MDS, aiming to alleviate anemia, reduce transfusion burden, and improve QoL ([Platzbecker 2019](#)).

ESAs, including recombinant EPO and darbepoetin, are widely recommended for patients with symptomatic anemia and an endogenous sEPO level below 500 U/L. Both European and US treatment guidelines recommend the use of ESAs for managing anemia in patients with LR-MDS ([Fenaux et al. 2021](#); [Malcovati et al. 2013](#)). These guidelines highlight the importance of assessing the patient's sEPO level before initiating therapy, as patients with sEPO levels below 500 U/L are more likely to respond positively to ESA treatment.

In a randomized trial, epoetin alfa reported improved erythroid responses (increased Hgb) compared to placebo (31.8% versus 4.4%, $p < 0.001$); however, mean duration of responses was 27.5 weeks, with not all responders maintaining response ([Fenaux et al. 2018](#)).

More recently luspatercept has been approved for front-line therapy by the FDA and EMA and is available in some countries. Luspatercept showed superiority over ESA in achieving RBC transfusion independence for consecutive ≥ 12 weeks with concurrent increase in mean Hgb ≥ 1.5 g/dL (60% versus 35%, $p < 0.0001$) in the initial 24 weeks on-trial, as reported from the COMMANDS trial. However, luspatercept efficacy was limited among patients who were ring sideroblast-negative (RS-negative) disease, with similar response reported in the ESA arm (47% versus 50%, respectively) ([Della Porta et al. 2024](#)). Furthermore, patients with HTB had lower responses than patients with LTB, 67% versus 48% respectively.

Assessing HRQoL is essential in clinical trials for lower-risk, transfusion-dependent MDS as treatment goals prioritize symptom relief and functional improvement. In this population, anemia-related fatigue, reduced physical functioning, and emotional distress significantly impact daily life and well-being ([Greenberg et al. 1997](#); [Oliva et al. 2011a](#)). Moreover, chronic RBC transfusions result in increased time in care, iron overload, and reduced independence, all of which can diminish HRQoL ([Abel et al. 2021](#); [Buckstein et al. 2023](#); [Diez-Campelo et al. 2024](#); [Jabbour et al. 2008](#); [Kaka et al. 2022](#); [Platzbecker et al. 2012](#); [Stojkov et al. 2023](#)). Treatments aimed at reducing transfusion dependence would be expected to improve HRQoL, and regulatory authorities emphasize the measurement of patient-reported outcomes, including HRQoL, in clinical trials for hematologic conditions (FDA Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Guidance for Industry. 2020; FDA Core Patient-Reported Outcomes in Cancer Clinical Trials: Guidance for Industry. October 2024; EMA Guideline on the evaluation of anticancer medicinal products in man. 2017). However, the temporary influence of RBC transfusions on anemia symptoms can complicate the assessment of HRQoL in MDS clinical trials ([Oliva et al. 2021](#)). Accounting for RBC transfusions, a post-hoc analysis of data from the COMMANDS trial found that participants treated with luspatercept had shortened time to confirmed improvement in fatigue and anemia symptoms through 48 weeks of treatment as compared to those treated with epoetin alfa ([Oliva et al. 2024](#)).

5.3 Inclusion Criteria

To be eligible to participate in this trial, an individual must meet all the following criteria:

1. Male or female participants aged ≥ 18 years or older at time of signing the informed consent form (ICF).
2. Able to understand the purpose and risks of the trial and voluntarily sign an ICF prior to any trial-related procedures being conducted and authorization to use protected health information and personal data in accordance to national and local privacy regulations.
3. Documented diagnosis of myelodysplastic syndrome(s) (MDS) according to WHO 2016 classification that meets International Prognostic Scoring System – Revised (IPSS-R) classification of very low-, low-, or intermediate-risk disease, confirmed by central laboratory independent reviewer prior to randomization. Hemoglobin (Hgb), platelet, and absolute neutrophil count (ANC) values should be collected >14 days after red blood cell (RBC) transfusion or >7 days after platelet transfusion, unless otherwise considered to be pretransfusion values.
4. Bone marrow $<5\%$ blasts in an evaluable bone marrow collected at screening and confirmed by central pathology independent reviewer.
5. Endogenous serum erythropoietin s (EPO) level of <500 U/L. Should be results from blood samples collected >14 days following an RBC transfusion to evaluate for eligibility unless considered pretransfusion values.
6. Participant requires RBC transfusion, as documented by the following criteria (Section 8.1.1.3). A transfusion requirement of 2 to 6 packed red blood cells (pRBCs) units/8 weeks confirmed for a minimum of 8 weeks immediately preceding randomization.
 - Hgb levels at the time of or within 3 days prior to administration of a RBC transfusion must have been ≤ 9.0 g/dL (5.6 mmol/L) with symptoms of anemia (or ≤ 7 g/dL [4.3 mmol/L] in the absence of symptoms) in order for the transfusion to be counted towards meeting eligibility criteria.
 - RBC transfusions administered when Hgb levels were >9.0 g/dL (or >7 g/dL in the absence of symptoms) and/or RBC transfusions administered for elective surgery, infections or bleeding events will not qualify as a required transfusion for the purpose of meeting eligibility criteria or stratification.
7. Hgb <11.0 g/dL (6.8 mmol/L) after last RBC transfusion preceding randomization. Local laboratory is acceptable to facilitate randomization.
8. Eastern Cooperative Oncology Group score of 0, 1, or 2.

5.4 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this trial:

1. Prior therapy with any of the following:

- a) Epoetin alfa
 - At the investigator's discretion in consultation with the medical monitor, may be allowed if received no more than 2 doses of only epoetin alfa ≥ 8 weeks prior to randomization. No other erythropoiesis-stimulating agent (ESA) agent is allowed.
- b) Darbepoetin.
- c) Granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor administered ≤ 8 weeks (56 days) prior to randomization unless given for treatment of febrile neutropenia.
- d) Immunomodulatory drug (IMiDs) including lenalidomide.
 - At the investigator's discretion in consultation with the medical monitor may be allowed if received ≤ 1 week of an IMiD ≥ 8 weeks prior to randomization.
- e) Hypomethylating agent.
 - At the investigator's discretion, in consultation with the medical monitor may be allowed if received no more than 2 doses ≥ 8 weeks prior to randomization.
- f) Luspatercept, sotatercept, imetelstat, or elritercept.
- g) Immunosuppressive therapy.
- h) Hematopoietic cell transplant.
- i) Iron chelation if administered ≤ 8 weeks prior to randomization. Participants on stable doses of iron chelation therapy for ≥ 8 weeks are allowed Vitamin B12 or folate therapy initiated within 4 weeks prior to randomization. Participants on stable replacement doses for ≥ 4 weeks and without ongoing concurrent vitamin B12 or folate deficiency are allowed.
- j) Androgen use within 8 weeks before randomization. Participants on stable androgen dosing for hypogonadism for ≥ 8 weeks are allowed.
- k) High-dose corticosteroid use within 4 weeks before randomization. Participants on stable chronic steroid doses of prednisone ≤ 10 mg/day or corticosteroid equivalent for ≥ 4 weeks are allowed. Other disease modifying treatments for autoimmune diseases may be allowed upon medical monitor review.
- l) Investigational agent or any other agent intended for treatment MDS treatment.

2. Diagnosed to have MDS associated with del(5q) cytogenetic abnormality or MDS unclassifiable according to WHO 2016 classification or secondary MDS.
3. Known history of diagnosis of acute myeloid leukemia (AML).
4. Anemia due to any other known cause including but not limited to thalassemia; hypothyroidism; due to iron, vitamin B12, vitamin B6, zinc, or folate deficiencies; autoimmune or hereditary hemolytic anemia; any type of known clinically significant bleeding or sequestration or drug induced anemia, hemolytic anemia, or bleeding events.
5. Clinically significant cardiovascular disease defined as:
 - a) New York Heart Association heart disease class III or IV.
 - b) Fridericia corrected QT (QTcF) interval >500 milliseconds during screening.
 - c) Uncontrolled arrhythmia, myocardial infarction, or unstable angina within 6 months before screening.
6. Known ejection fraction <35%, confirmed by a local echocardiogram performed during screening, or a previously performed echocardiogram if collected within 6 months before screening.
7. Medical history of thromboembolic events within 6 months before screening, including history of cerebrovascular accident (including ischemic, embolic, and hemorrhagic cerebrovascular accident), transient ischemic attack, deep venous thrombosis (DVT; including proximal and distal), pulmonary or arterial embolism, arterial thrombosis or other venous thrombosis. Participants with prior superficial thrombophlebitis are allowed.
8. Uncontrolled hypertension, defined as repeated elevations of systolic blood pressure of ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg despite adequate treatment.
9. Prior history of malignancies, other than MDS. Participants who are free of other malignant disease for ≥ 3 years and have completed treatment, including maintenance are allowed. Participants with a history or concurrent diagnosis of the following conditions are allowed if not requiring systemic therapy:
 - a) Basal or squamous cell carcinoma of the skin;
 - b) Carcinoma in situ of the cervix;
 - c) Carcinoma in situ of the breast; and/or
 - d) Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, node, metastasis [TNM] clinical staging system).
10. History of solid organ or bone marrow transplantation.
11. Active infection requiring intravenous antibiotics within 28 days or oral antibiotics within 14 days before randomization.

12. Known positive for HIV, active infectious hepatitis B virus (HBV), or active infectious hepatitis C virus (HCV). Participants without known positive history of HIV, HBV, and/or HCV do not require further testing, unless testing is mandated per local guidelines.
13. Body mass index ≥ 40 kg/m².
14. Major surgery within 28 days before randomization.
15. New-onset seizures or poorly controlled seizures within 12 weeks prior to randomization are excluded from trial participation.
16. History of allergy/anaphylaxis to investigational product (including epoetin alfa) excipients (refer to the current elritercept investigator's brochure for a list of excipients) or recombination proteins.
17. History of pure red cell aplasia and/or antibody against erythropoietin (EPO).
18. Any of the following laboratory abnormalities:
 - a) ANC $< 500/\mu\text{L}$ ($0.5 \times 10^9/\text{L}$).
 - b) Platelet count $< 50,000/\mu\text{L}$ ($50 \times 10^9/\text{L}$) or $\geq 450,000/\mu\text{L}$ ($450 \times 10^9/\text{L}$).
 - c) Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 3 \times$ upper limit of the normal (ULN).
 - d) Total bilirubin $\geq 2 \times \text{ULN}$. Participants with known history of Gilbert syndrome with unconjugated bilirubin $< 3 \times \text{ULN}$ are allowed. Higher levels if attributed to active RBC precursor destruction within the bone marrow (ineffective erythropoiesis) may be allowed upon medical monitor review.
 - e) Estimated glomerular filtration rate < 30 mL/min/1.73 m² as determined by the Chronic Kidney Disease Epidemiology (CKD-EPI) collaboration equation ([Delgado et al. 2021](#); [Kramer et al. 2022](#)).
 - f) Ferritin ≤ 50 $\mu\text{g/L}$.
 - g) Folate ≤ 2.0 ng/mL.
 - h) Vitamin B12 ≤ 200 pg/mL.
19. Ongoing participation in another interventional clinical trial.
20. Participant is unwilling or in the opinion of the investigator the participant is unable to comply with the requirements of the protocol.
21. Is a participant of childbearing potential (POCBP) but does not agree to use at least 1 form of highly effective contraception from the time of signing the ICF until at least 60 days after the last dose of trial intervention (see Section [13.1](#) for details).
22. Participants of male birth who are fertile and who have partners of childbearing potential, who do not agree to use acceptable barrier contraception, that is, a male condom during the

entire trial intervention period until at least 60 days after the last dose of trial intervention (see Section 13.1 for details).

23. If applicable, participant with a positive serum pregnancy test during the screening period or known to be pregnant or a lactating participant who does not agree to forego breastfeeding during the entire trial intervention period until at least 60 days after the last dose of trial intervention.
24. For Participants in France: Persons under court protection, persons not affiliated with a social security system, and protected adults (per applicable French law [Art. L. 1121-6, Art. L. 1121-8, Art. L. 1121-8-1]).

5.5 Lifestyle Considerations

Participants must follow the contraception use rules specified in Exclusion Criterion 21 and Exclusion Criterion 22, as applicable.

5.6 Screen Failures

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (for example, blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).

Participant identification numbers assigned to participants who do not meet eligibility criteria should not be reused.

Screen failures will be captured and tracked in the IRT and EDC systems.

5.6.1 Screen Failure Categorization, Information Collection, and Other Procedures

An individual who has provided informed consent to participate in the trial and has not been randomized may be categorized as a screen failure for any of the following reasons:

- Did not meet eligibility criteria.
- AE.
- Lost to follow-up.
- Pregnancy.
- Withdrawal by participant.
- Trial terminated by sponsor.

- Other (specify).

Participants are **not** considered screen failures if they were randomized but not treated.

Information about screen failures should be collected via the eCRFs, including participant identification, screening disposition (including the reason for screen failure), demography, inclusion/exclusion criteria, and AEs (if applicable). If a potential participant experiences an SAE during screening, all of the participant's screening eCRFs must be available for collection.

5.6.2 Rescreening

Participants who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Rescreened participants must be reconsented and assigned a new participant number. If the participant is rescreened, the bone marrow collection and blood for disease assessment does not need to be repeated if disease confirmation per IPSS-R was completed within 6 months of randomization. Echocardiogram does not need to be repeated if the existing echocardiogram within 6 months meets eligibility requirements. All other Screening assessments should be repeated to verify trial eligibility.

6.0 TRIAL INTERVENTION AND CONCOMITANT THERAPY

This trial has the following IMPs:

- Elritercept (experimental therapy).
- Epoetin alfa (comparator).

It uses no auxiliary medicinal product(s).

These trial interventions are detailed in Section 6.1.

6.1 Description of Trial Intervention

Refer to the current elritercept IB for treatment formulation, including excipients. Elritercept will be supplied to the trial site's pharmacy for preparation for SC administration. Refer to the Pharmacy Manual for details.

Table 6.a Table of Trial Interventions

Product name	Elritercept	Epoetin alfa
Designation	IMP	IMP (comparator)
Identification in the Protocol	Elritercept (TAK-226, KER-050)	INN/active substance: epoetin alfa
European MA	No	Yes (centralized): a product authorized in EU will be used for the selected INN for EU countries.
Used Within MA	NA	Yes
ATC Code	NA	B03XA01

Table 6.a Table of Trial Interventions

Product name	Elritercept	Epoetin alfa
Active Substance	Elritercept	Epoetin alfa
Dose Formulation	100 mg/mL, 200 mg Vial	In EU: Pre-Filled Syringes or Pens of various approved strengths to achieve target dose. Outside of EU: Pre-Filled Syringes, pens, or vials where applicable.
Dose Strength(s)	Starting dose is 3.75 mg/kg	Starting dose is 450 IU/kg
Route of Administration	SC	SC
Dosage Level(s)	Starting Dose: 3.75 mg/kg Dose Escalation: 5.0 mg/kg	Starting Dose: 450 IU/kg (Rounded up to next 2000 IU) Dose Escalation +1: 787.5 IU/kg (Rounded up to next 2000 IU) Dose Escalation +2: 1050 IU/kg (Rounded up to next 4000 IU for dosing >56,000 IU)
Dose Regimen	Once every 4 weeks	Once every week
Duration	Up to 5 years from randomization.	Up to 5 years from randomization.
Arm (participants receiving the medicinal product)	Participants randomized to receive elritercept.	Participants randomized to receive epoetin alfa.
Sourcing	Provided centrally by the sponsor	Provided centrally, locally by the sponsor, or by trial site where allowed

6.2 Rationale for Trial Intervention

Elritercept (KER-050, TAK-226) is an IMP being developed for the treatment of anemia in adults with very low-, low-, or intermediate-risk MDS, classified as LR-MDS. In MDS, somatic mutations in progenitor cells result in incomplete maturation and/or differentiation within the hematopoiesis pathway, resulting in ineffective hematopoiesis and cytopenia(s). Dysregulated TGF- β superfamily signaling has been identified as a contributing factor to the ineffective hematopoiesis in MDS.

Elritercept is a recombinant fusion protein designed to inhibit signaling by select TGF- β superfamily ligands, including activin A, activin B, GDF 8, and GDF 11. This inhibition normalizes signaling and stimulates the maturation and differentiation of early- and late-stage erythroid and megakaryocyte precursors in the bone marrow, potentially restoring effective hematopoiesis.

The signaling of TGF- β superfamily ligands (including activin A, activin B, GDF8, and GDF11) occurs through 1 of 2 canonical pathways: SMAD1/5/9 or SMAD2/3. Specifically, the bone morphogenetic protein ligand family predominantly signals through SMAD1/5/9 and is regarded as a proerythropoiesis signal ([Blank and Karlsson 2011](#); [Massagué et al. 2005](#);

[Paulson et al. 2011](#)). In contrast, signaling through SMAD2/3 by activins and GDFs induces quiescence, self-renewal, and reduced hematopoietic maturation, where progenitor cells are stopped from progressing through later stages of hematopoiesis ([Brenet and Scandura 2015](#); [Hinge and Filippi 2016](#); [Yamazaki et al. 2009](#)). Homeostasis of this process is essential to ensure all cell types are properly replenished in the blood. Overactivation of one pathway can lead to ineffective hematopoiesis and peripheral blood cytopenias observed in patients with MDS ([Verma et al. 2020](#); [Zingariello et al. 2013](#)).

Elritercept is an investigational modified activin receptor type IIA ligand trap designed to selectively inhibit ligands that activate SMAD2/3 signaling and thereby rebalance TGF- β superfamily signaling. Elritercept exhibits substantial inhibition of activin A (with half-maximal inhibitory concentration of 120 ng/mL), which may confer additional benefits beyond restoring effective hematopoiesis to more broadly correct MDS pathophysiology. Additional details on the mode of action for elritercept are provided in the current elritercept IB.

Based on the ongoing phase 2 trial (KER-050-MD-201), preliminary PK/PD as well as exposure-efficacy analyses, the proposed starting dosing regimen for elritercept is 3.75 mg/kg administered SC Q4W. Dose modification is specified for insufficient response or for nonhematologic and hematologic adverse reactions ([Table 6.b](#)). The starting dose can be up-titrated to 5.0 mg/kg Q4W or down-titrated to 2.5 mg/kg Q4W based on the dose modification guidelines. Elritercept should be discontinued for participants still unable to tolerate the drug after down-titration to 2.5 mg/kg Q4W.

6.3 Dosing and Administration

6.3.1 Elritercept Dosing

The starting dose for elritercept in participants with LR-MDS is 3.75 mg/kg. Elritercept is administered SC Q4W.

No more than 2 days before each elritercept administration (Day 1 of each cycle), collect a blood sample for hematology (CBC with differential) to assess Hgb and platelet levels to ensure dose modification rules are followed.

Dosing is based on participant weight. Body weight must be confirmed no more than 3 days before trial intervention administration to calculate the dose. Weight will be reassessed in the event of a dose delay (>4 weeks from prior dose) at restart of treatment. Changes of body weight of $\leq \pm 5\%$ do not require a dose adjustment. If the participant weight is not within 5% of the weight used for the prior dosing calculation, a new dose must be recalculated based on the current weight. This updated dose must be prepared for administration.

Record date, dose, site of administration, and time of elritercept administration in eCRF.

The recommended SC injection site is the abdomen with rotation amongst quadrants to accommodate volume of injections and/or alternate between different visits.

If it is clinically indicated for a participant to require a RBC transfusion on the day of dosing, the transfusion must be completed prior to trial intervention administration (See Section 8.2.1).

Refer to Section 6.3.1.1, and Table 6.b for dose-modification and treatment-discontinuation guidelines. Refer to Section 6.3.1.2, and Table 6.c for dose-reduction guidelines.

Refer to the current elritercept IB for further details.

6.3.1.1 Elritercept Dosing Modification

Dose modification decisions will be made by the treating investigator in accordance with the guidelines presented in Table 6.b and Table 6.c.

Table 6.b Elritercept Dose Modification and Discontinuation Guidelines

Event on the Day of Dosing (assessed before each dose administration) ^{a,b}	Action
Any Grade ≥ 3 treatment-related injection site reaction, allergic reaction, anaphylaxis, or other hypersensitivity reaction	Discontinue treatment
Any treatment-related Grade ≥ 3 AE, including any new or recurrent AE excluding events of Hgb increase or Platelet increase ^{c,d,e} .	Dose delay until resolved to Grade ≤ 1 or baseline and then reduce dose as outlined in Table 6.c based upon safety ^f
Any non-hematologic treatment-related Grade 4 AE ^e	Discontinue treatment
Dose delay exceeding 90 consecutive days (except if due to an elevated Hgb level or platelet count)	Discontinue treatment
Increased Hgb ≥ 2.0 g/dL compared with predose Hgb of previous dosing day AND participant has not received a transfusion in the past 28 days	Reduce dose as outlined in Table 6.c based upon safety ^f If at dose level 2.5 mg/kg, at the discretion of investigator may delay dosing. <i>In addition, if predose Hgb ≥ 12.0 g/dL, dose delay until Hgb ≤ 11.0 g/dL, and then reduce dose as outlined in Table 6.c upon restart</i>
Predose Hgb ≥ 12.0 g/dL	Dose delay until Hgb ≤ 11.0 g/dL and then restart at the same dose or a reduced dose at the discretion of the investigator
For participants with baseline/C1D1 platelet count $< 400 \times 10^9/L$, if platelet count increases to $> 500 \times 10^9/L$ OR For participants with baseline/C1D1 platelet count 400 to $450 \times 10^9/L$, if platelet count increases by $> 100 \times 10^9/L$ (500 to $550 \times 10^9/L$) over C1D1	Dose delay until platelet count $\leq 450 \times 10^9/L$ and then restart at the same dose (or a reduced dose if dose reduction is warranted in the opinion of the investigator) If platelet count increase (thrombocytosis) recurs during subsequent cycle, reduce dose as outlined in Table 6.c ^f

^a Dose reductions will be the decision of the treating investigator. The sponsor will be made aware of the dose change via updates in IRT and the dosing injection eCRF.

^b Dose reductions for safety are not optional if driven by parameters noted.

^c Related to trial therapy in the opinion of the investigator.

^d Includes mean systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg.

Table 6.b Elritercept Dose Modification and Discontinuation Guidelines

Event on the Day of Dosing (assessed before each dose administration) ^{a,b}	Action
---	--------

^e Severity will be assessed according to NCI-CTCAE version 5.0 or higher, wherever possible.

^f Dose reductions are allowed to 2.5 mg/kg. If this dose is not tolerated (that is, further dose reduction required), treatment must be discontinued.

6.3.1.2 Elritercept Dose Reduction

Elritercept dose may be down-titrated to 2.5 mg/kg Q4W, (see [Table 6.c](#)) as required due to increases in hematology parameters (including increased Hgb or platelet count) or TEAEs based on the dose-modification guidelines (refer to Section 6.3.1.1). Criteria for dose modification and discontinuation of elritercept are presented in [Table 6.b](#) and Section 7.1.

Table 6.c Dose Reduction and Escalation Guidelines

Dose Reduction Level -2	Dose Reduction Level -1	Starting Dose	Dose Escalation Level +1
Discontinue	2.5 mg/kg	3.75 mg/kg	5.0 mg/kg

6.3.1.3 Elritercept Dose Up-Titration

All participants will be assessed for up-titration up to 5.0 mg/kg after 2 consecutive doses starting at C3D1 (Week 9) as deemed appropriate to maintain Hgb levels within the target range of 10 g/dL to 12 g/dL (6.2 mmol/L to 7.5 mmol/L) independent of transfusions per investigator discretion.

Dose **up-titration** up to a maximum of 5.0 mg/kg (refer to [Table 6.c](#)) is allowed if all of the following criteria are met:

1. Hgb level is <11 g/dL (6.8 mmol/L). For participants with RBC transfusion within prior 7 days, if the Hgb level is ≤12 g/dL (7.5 mmol/L) the dose may still be adjusted.
2. Hgb level increase is ≤1.0 g/dL (0.6 mmol/L) compared to the Hgb sample taken prior to the previous elritercept dose. If the Hgb level increase is >1.0 g/dL due to the influence of transfusions, the dose may still be adjusted.
3. The 2 most recent prior elritercept administrations assessed must be at the same dose level.
4. Must not have met protocol dose delay and/or reduction criteria in the 2 most recent elritercept administrations (exception of dose delay required due to influence of RBC transfusions).

Up-titration is not permitted if any of the following criteria are met:

- Criteria for dose delay or reduction as noted in [Table 6.b](#).

- Currently receiving maximum dose level of 5.0 mg/kg Q4W.
- Prior dose reduction for safety, and up-titration is considered not appropriate by the investigator and/or upon review with the medical monitor.

If the participant experienced a dose reduction, after 2 consecutive doses at a given dose level, up-titration to the next higher dose level as outlined in [Table 6.c](#) may be considered with caution.

Investigators may confer with the sponsor to determine when and whether up-titration is appropriate for an individual participant.

6.3.1.4 *Elritercept Up-Titration to a Higher Dose After Dose Reduction*

If a participant experienced a dose reduction due to increased Hgb, increased platelet count, or TEAEs ([Table 6.b](#)), up-titration to a higher dose should be considered with caution. In situations where the parameters leading to dose reduction have resolved and are not expected to reoccur, up-titration by one dose level ([Table 6.c](#)) is permitted. Participants should have received a dose for ≥ 2 cycles before up-titration and have met the criteria outlined in Section [6.3.1.1](#).

Investigators may confer with the sponsor to determine when and whether up-titration is appropriate for an individual participant.

6.3.2 **Epoetin Alfa Dosing**

The starting dose of epoetin alfa is 450 IU/kg, rounded up to the next nearest 2000 IU's, not to exceed a maximum dose of 40,000 IU (refer to [Table 6.e](#)). Epoetin alfa is administered SC. Epoetin alfa dosing is repeated once every week (7 days; QW). No more than 2 days before each epoetin alfa administration collect a blood sample for hematology (CBC with differential) to assess Hgb and platelet levels to ensure dose modification rules are followed; local Hgb values are acceptable when dosing does not occur on site and not required if dosed at home.

Dosing is based on participant weight. Every fourth week, the dose is reassessed based on the participant weight measured up to 72 hours before epoetin alfa administration. Weight will be reassessed in the event of a dose delay at restart of treatment. Changes of body weight of $\leq \pm 5\%$ do not require a dose adjustment. If the participant weight is not within 5% of the weight used for the prior dosing calculation, a new dose must be recalculated based on the current weight. This updated dose must be prepared for administration for this and the subsequent 3 weekly doses.

Epoetin alfa will be administered as a SC injection by site-designated staff on Day 1 of every cycle and in the event dose adjustment is required. Self-administration or administration by a home health service provider is permitted between the monthly (Cycle Day 1) dosing visits at the discretion of the investigator, if consistent with local practice and ensuring all other required trial assessments for the visit are completed per SOA (See Section [1.3](#)).

Recommended SC injection site is the abdomen with rotation amongst quadrants to accommodate volume of injections and/or alternate between different visits. Administration of epoetin alfa will be documented in the participant's source record. Compliance of

self-administration of epoetin alfa will be monitored via the use of a medication diary card. Record date, dose, site of administration, and time of epoetin alfa administration in eCRF.

If it is clinically indicated for a participant to require a RBC transfusion on the day of dosing, the transfusion must be completed prior to trial intervention administration (Section 8.2.1.2).

6.3.2.1 *Epoetin Alfa Dose Modification*

The epoetin alfa dose may be up-titrated after 8 doses as of dosing visit C3D1 (W9D1) and every cycle (4th dose) thereafter as deemed appropriate to maintain Hgb target levels and for lack of efficacy per the investigator discretion and/or upon review with the medical monitor.

Individual epoetin alfa doses according to body weight will be rounded up:

- to the next 2000 IU dose level for Starting Dose Level and Dose Level -1
- to the next 2000 IU for Dose Level +1 and 4000 IU for Dose Level +2 for doses exceeding a calculated dosing of 56,000 IU according to body weight with maximum total dose of 80,000 IU

Since dosing is according to body weight, weight is to be assessed in the event of a dose delay at restart of treatment. Changes of body weight of $\leq \pm 5\%$ do not require a dose adjustment.

6.3.2.2 *Epoetin Alfa Dose Reduction*

Dose delay and/or reduction or discontinuation may be required due to increased Hgb or AEs. For details on dose modification guidance for epoetin alfa please refer to [Table 6.d](#).

If dose delay for toxicity is >90 days, treatment must be permanently discontinued, unless the treatment gap was due to an elevated Hgb or platelet count.

Table 6.d Epoetin Alfa Dose Modification and Discontinuation Guidelines

Event on the Day of Dosing (assessed before each dose administration) ^{a,b}	Action
Any Grade ≥ 3 treatment-related injection site reaction, allergic reaction, anaphylaxis, or other hypersensitivity reaction	Discontinue treatment
Any treatment-related Grade ≥ 3 AE, including any new or recurrent AE excluding events of Hgb increase or Platelet increase ^{c,d,e}	Dose delay until resolved to Grade ≤ 1 or baseline and then reduce dose as outlined in Table 6.e based upon safety ^f
Any non-hematologic treatment-related Grade 4 AE ^e	Discontinue treatment
Dose delay exceeding 90 consecutive days (except if due to an elevated Hgb level or platelet count)	Discontinue treatment
Severe cutaneous adverse reactions including Erythema multiforme and Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis	Discontinue treatment immediately if signs and symptoms suggestive of these reactions appear
PRCA	Discontinue treatment

Table 6.d Epoetin Alfa Dose Modification and Discontinuation Guidelines

Event on the Day of Dosing (assessed before each dose administration) ^{a,b}	Action
Increased Hgb ≥ 2.0 g/dL compared with predose Hgb of previous dosing day AND participant has not received a transfusion in the past 28 days	Reduce dose as outlined in Table 6.e based upon safety ^f If at dose level 337.5 IU/kg, at the discretion of investigator may delay dosing. <i>In addition, if predose Hgb ≥ 12.0 g/dL, dose delay until Hgb ≤ 11.0 g/dL, and then reduce dose as outlined in Table 6.e upon restart</i>
Predose Hgb ≥ 12.0 g/dL	Dose delay until Hgb ≤ 11.0 g/dL and then restart at the same dose or a reduced dose at the discretion of the investigator
For participants with baseline/C1D1 platelet count $< 400 \times 10^9/L$, if platelet count increases to $> 500 \times 10^9/L$ OR For participants with baseline/C1D1 platelet count 400 to $450 \times 10^9/L$, if platelet count increases by $> 100 \times 10^9/L$ (500 to $550 \times 10^9/L$) over C1D1	Dose delay until platelet count $\leq 450 \times 10^9/L$ and then restart at the same dose (or a reduced dose if dose reduction is warranted in the opinion of the investigator) If platelet count increase (thrombocytosis) recurs during subsequent cycle, reduce dose as outlined in Table 6.e ^f

^a Dose reductions will be the decision of the treating investigator. The sponsor will be made aware of the dose change via updates in IRT and the dosing injection eCRF.

^b Dose reductions for safety are not optional if driven by parameters noted.

^c Related to trial therapy in the opinion of the investigator.

^d Includes mean systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg.

^e Severity will be assessed according to NCI-CTCAE version 5.0 or higher, wherever possible.

^f Dose reductions are allowed to 337.5 IU/Kg. If this dose is not tolerated (that is, further dose reduction required), treatment must be discontinued.

Table 6.e Epoetin Alfa Dose Reductions and Escalations

Dose Reduction Level -1	Starting Dose	Dose Escalation Level +1	Second Dose Escalation Level +2
337.5 IU/Kg Rounded up to next 2000 IU Max. 40,000 IU	450 IU/kg Rounded up to next 2000 IU Max. 40,000 IU	787.5 IU/kg Rounded up to next 2000 IU Max. 80,000 IU	1050 IU/kg Rounded up to next 4000 IU for dosing $> 56,000$ IU Max. 80,000 IU

6.3.2.3 Epoetin Alfa Dose Up-Titration

All participants will be assessed for up-titration after 8 consecutive doses starting at C3D1 as deemed appropriate to maintain Hgb levels within the target range of 10 g/dL to 12 g/dL (6.2 mmol/L to 7.5 mmol/L) independent of transfusions per investigator discretion.

CONFIDENTIAL

Dose up-titration in a stepwise approach according to the dose escalation levels in [Table 6.e](#) is allowed if all of the following criteria are met:

1. Hgb levels is <11 g/dL (6.8 mmol/L). For participants with RBC transfusion within prior 7 days, if the Hgb level is ≤ 12 g/dL (7.5 mmol/L) the dose may still be adjusted.
2. Hgb level increase is ≤ 1.0 g/dL (0.6 mmol/L) compared to the Hgb sample taken prior to the previous epoetin alfa dose. If the Hgb level increase is >1.0 g/dL due to the influence of transfusions, the dose may still be adjusted.
3. The 4 most recent prior epoetin alfa administrations assessed must be at the same dose level.
4. Must not have met protocol dose delay and/or reduction criteria in the 4 most recent epoetin alfa administrations (exception of dose delay required due to influence of RBC transfusions).

Up-titration is not permitted if any of the following criteria are met:

- Criteria for dose delay or reduction as noted in [Table 6.d](#).
- Currently receiving maximum dose level of 1050 IU/kg (80,000 IU).
- Prior dose reduction for safety, and up-titration is considered not appropriate by the investigator and/or upon review with the medical monitor.

If the participant experienced a dose reduction, after receiving 4 consecutive doses over a minimum of 4 weeks at a given dose level, up-titration to the next higher dose level as outlined in [Table 6.e](#) may be considered with caution.

6.3.2.4 Self Administration of Epoetin Alfa

Self-administration of epoetin alfa is allowed and is defined as administration by the participant or their caregiver at the investigational site or in an offsite location.

Self-administration will be permitted after a participant (and/or their caregiver) has received appropriate training by the investigator or designee and has demonstrated their understanding of self-administration. Participants may initiate self-administration after receiving the first 2 doses of epoetin alfa administered by site-designated staff at the trial site. The participant is required to return to the site for visits as outlined in the SoA ([Table 1.c](#)). At these on-site visits, the participants (or caregiver) may continue to self-administer epoetin alfa or may opt to have the product administered by trial personnel or healthcare provider.

The investigator or designee will train participants (and/or caregivers) who elect to self-administer investigational product on the following:

- The participant's (or caregiver's) transportation of investigational product using a site-provided cooler, and the recommended storage conditions of epoetin alfa when stored at an offsite location.
- Maintenance of accurate records regarding each administration of epoetin alfa including supply identification (that is, lot/kit number), date and time of injection, injection site

CONFIDENTIAL

location, injection infusion time, and if applicable, any reason the self-administration could not be completed as instructed.

- Retention of all used and unused investigational product for drug accountability purposes.
- Additional information, as provided in the Pharmacy Manual.

If a participant (or caregiver) is self-administering epoetin alfa at home or another offsite location, site personnel will perform a site check-in (within 3 days after the trial day) to ensure that self-administration of epoetin alfa has occurred as scheduled. During this site check-in, the site will also solicit for any injection site reactions angioedema attacks not already reported by the participant and collect information on AEs and concomitant medications. The preferred method of site contact is a telephone call; however, alternate methods of contact may be considered as site policies permit.

6.4 Treatment of Overdose

6.4.1 Elritercept Overdose

An overdose is defined as follows:

- On a per-dose basis, a dosing error leading to an excess of 10% over the protocol-specified dose assigned to a given participant, regardless of any associated AE or sequelae.
- On a schedule or frequency basis, a scheduling error leading to 2 administrations of trial intervention with an interval of <21 days.
- Complete data about trial intervention administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be recorded on the paper Special Situation Report form.

In the event of an overdose, the participant should be monitored as appropriate and should be treated symptomatically as necessary.

Overdose, either accidental or intentional, whether it is associated with an AE, should be recorded on the paper Special Situation Report form. Any sequela of an accidental or intentional overdose of trial intervention should be reported as an AE on the paper Special Situation Report form. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. Closely monitor the participant for any AE/SAE and laboratory abnormalities until the resolution of the event.

There is no known specific antidote for elritercept overdose. The management of overdose should depend on the severity of the clinical status and the judgment and experience of the investigator. In the event of an overdose, participants should be treated symptomatically accordingly to local guidelines. Additional supportive care should be provided as necessary at the investigator's discretion.

6.4.2 Epoetin Alfa Overdose

On a per dose basis, an overdose for epoetin alfa is defined as the following amount over the protocol-specified dose of epoetin alfa assigned to a given participant, regardless of any associated AEs or sequelae.

- SC injection 10% over the protocol-specified dose.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the paper Special Situation Report form.

The therapeutic margin of epoetin alfa is very wide. Overdosage of epoetin alfa may produce effects that are extensions of the pharmacological effects of the hormone. In the event of an overdose, participants should be treated symptomatically according to local guidelines. Additional supportive care should be provided as necessary at the investigator's discretion.

Overdose, either accidental or intentional, whether it is associated with an AE, should be recorded on the paper Special Situation Report form. Any sequela of an accidental or intentional overdose of trial intervention should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. Closely monitor the participant for any AE/SAE and laboratory abnormalities until the resolution of the event.

There is no known specific antidote for epoetin alfa overdose. The management of overdose should depend on the severity of the clinical status and the judgment and experience of the investigator. In the event of an overdose, participants should be treated symptomatically according to local guidelines. Additional supportive care should be provided as necessary at the investigator's discretion.

6.5 Preparation, Handling, Storage, and Accountability

6.5.1 Preparation of Trial Intervention

Please refer to the pharmacy manual for instructions related to the preparation of elritercept for administration in participants.

For epoetin alfa, please refer to the pharmacy manual or local prescribing information for administration in participants.

6.5.2 Handling and Storage of Trial Intervention

Elritercept will be stored in refrigerated (2°C to 8°C) conditions by the trial site personnel according to the documentation provided with the trial materials. Access must be limited to authorized site personnel.

All trial treatment must be at a controlled temperature as indicated on the clinical trial labels and in the pharmacy manual. Temperature monitoring is required at the storage location to ensure that trial treatment is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the duration of the trial and that records are maintained. Refer to the trial pharmacy manual for additional storage instructions.

The sponsor reserves the right to inspect the trial treatment storage area before and during the trial. A written record will be made of the storage conditions of the trial materials and retained for the investigator's Site File.

Elritercept will be labeled in accordance with text that is in regulatory compliance with the participating country. Refer to the pharmacy manual for further details on labeling of elritercept.

Epoetin alfa, where provided centrally by the sponsor, should be stored as per pharmacy manual or per local prescribing information. Epoetin alfa, where provided centrally by the Sponsor, will be labeled in accordance with text that is in regulatory compliance with the participating countries. Refer to the pharmacy manual for further details on labeling of centrally supplied epoetin alfa.

6.5.3 Accountability of Trial Intervention

The investigator is responsible for elritercept and sponsor supplied epoetin alfa accountability, reconciliation, and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the investigator or site-designated staff must maintain study treatment-accountability records throughout the course of the trial. The amount of trial intervention received from the sponsor, and the amount supplied and/or administered to participants, will be documented.

Dispensing of elritercept and sponsor supplied epoetin alfa will be carefully recorded on appropriate accountability forms and will be verified by the trial monitor during monitoring visits.

The accountability logs should include dates, quantities, batch numbers, expiration dates, and any unique pack numbers assigned to the trial intervention and/or participant. The accountability logs will also include general details related to the study, including the protocol number, sponsor, and the investigator.

The trial monitor will review the trial intervention-accountability logs and reconcile with all trial intervention, used and unused. After reconciliation, all trial intervention, unused and used/empty containers, will be returned to the drug depot or destroyed on site with prior approval from the sponsor. Refer to the pharmacy manual for further details on trial intervention destruction and return.

6.6 Participant Assignment, Randomization, and Blinding

6.6.1 Participant Assignment

This is an open-label trial. Participant assignment will follow the randomization plan.

6.6.2 Randomization and Stratification

This is an active-controlled trial. The treatment assigned to individual participants is determined by a computer-generated randomization schedule.

Randomization will be stratified for participants who have provided informed consent and meet all eligibility criteria during the screening period according to their RS status (RS+ versus RS- disease) and baseline transfusion burden (LTB versus HTB) as defined in inclusion criteria.

- RBC transfusion burden at baseline

LTB: 2 to 3 pRBC units/8 weeks

HTB: 4 to 6 pRBC units/8 weeks

- RS status at baseline (with RS+ defined as RS $\geq$ 15% of erythroid precursors in bone marrow or $\geq$ 5% (but <15%) if SF3B1 mutation is present).

RS+

RS-

- Endogenous sEPO level at baseline.

$\leq$ 200 U/L

$>$ 200 U/L

Individual participant treatment assignment is automatically assigned using the IRT.

All participants will be centrally assigned to randomized trial intervention using an IRT. Before the trial is initiated, the telephone number and call-in directions for the IRT and/or the log-in information and directions for the IRT will be provided to each site. The site will contact the IRT before the start of trial intervention administration for each participant. The site will record the intervention assignment on the applicable eCRF, if required. Randomization should occur on the same day as the start of treatment but may occur up to 3 business days beforehand.

In addition, the investigator will be provided with the baseline Hgb threshold determined as the mean values from the Hgb values collected during the 8 weeks prior to randomization.

6.6.3 Blinding and Unblinding

Not applicable. This is an open-label trial; investigators and participants will know the individual treatment assignments.

6.7 Trial Intervention Compliance

Elritercept will be administered as a SC injection at the clinical site by the site-designated staff. Therefore, it is unnecessary to monitor participant compliance with the elritercept treatment regimen.

Epoetin alfa will be administered as a SC injection by the site-designated staff or, at the investigator's discretion and per local practice, by a home health service provider or be self-administered by the participant at specified visits. There is no need to monitor for participant compliance with epoetin alfa if the treatment is administered at the site or by a home health service provider. If epoetin alfa is self-administered, then participant compliance will be monitored via the use of a medication diary card.

The investigator or designee is responsible for accounting for all IPs (elritercept and epoetin alfa) administered during the trial. Accurate recording of all IP administration will be made in the appropriate section of the participant's eCRF and source documents.

6.8 Concomitant Therapy

If the use of any concomitant treatment or procedure becomes necessary (for example, for treatment of an AE), the treatment and administration details must be recorded in the source documents and the eCRF. The medical monitor should be notified once it is realized that any prohibited medication was administered to any participant in order to assess the participant's eligibility to continue in the trial.

6.8.1 Prohibited Concomitant Therapy

The following therapies are prohibited during the trial:

- Myeloid growth factors (such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) except in cases of neutropenic fever, severe neutropenia, or as clinically indicated per label.
- Luspatercept, sotatercept, imetelstat,
- Lenalidomide, other iMiDS or hypomethylating agents.
- ESAs such as, EPO, darbepoetin, and other erythropoietic growth factors (for example, interleukin-3) or other therapies for MDS.
- TPO, TPO-receptor agonists, and TPO analogs.
- Systemic anticancer therapy, including cytotoxic, chemotherapeutic, immunologic, and biologic therapies.
- Systemic radiotherapy.
- Any investigational agent other than the trial intervention, including agents that are commercially available for indications other than MDS that are under investigation for the treatment of MDS.

CONFIDENTIAL

- Hydroxyurea.
- Androgens, unless to treat hypogonadism.
- High-dose, chronic steroid therapy (exceptions: chronic steroids at doses of prednisone ≤ 10 mg/day or corticosteroid equivalent, topical steroid for preexisting skin conditions and any short-term steroid dose required to treat AEs are allowed).
- Oral retinoids (topical retinoids are permitted).
- Arsenic trioxide.
- Interferon.
- Any medication(s) or treatments, other than RBC and platelet transfusions and iron chelation therapy, administered for the purpose of treating MDS or MDS-associated cytopenias.

6.8.2 Permitted Concomitant Therapy

6.8.2.1 RBC Transfusion

Concurrent treatment for anemia with RBC transfusions is allowed at the discretion of the investigator for low Hgb levels, symptom(s) associated with anemia (for example, hemodynamic or pulmonary compromise requiring treatment) or comorbidity. Criteria for RBC transfusions should be consistently applied throughout the trial as described in Section 8.2.1.

For any RBC transfusions received during the trial, a pre-transfusion Hgb value no more than 72 hours (3 days) prior to transfusion should be collected as specified in Section 8.2.1.2, and recorded in the eCRF.

If it is clinically indicated for a participant to require a RBC transfusion on the day of dosing, the transfusion must be completed prior to trial intervention administration (See Section 8.2.1).

6.8.2.2 Platelet Transfusion

Participants may receive platelet transfusions as needed for bleeding symptoms or for platelet counts $\leq 10 \times 10^9$ /L, or higher at the discretion of the investigator. For any platelet transfusion received during the trial, a pre-transfusion platelet level should be collected as specified in Section 8.2.1.3 and recorded in the eCRF. Record the date, the total units and the indication for the platelet transfusion.

If it is clinically indicated for a participant to require a platelet transfusion on the day of dosing, the transfusion must be completed prior to trial intervention administration.

6.8.2.3 Iron Chelation Therapy

Concurrent treatment with iron chelation therapy during the treatment period is allowed at the discretion of the investigator and is recommended to be used per product label. The investigator

is responsible for ensuring that iron chelation therapy is administered in accordance with local prescribing information, including dose modifications and monitoring for renal and hepatic impairment. If a participant meets criteria for discontinuation or interruption of iron chelation therapy per product label and/or in accordance with local treatment guidelines, iron chelation therapy will be discontinued or interrupted accordingly.

6.8.3 Rescue Therapy

Not applicable.

6.9 Management of Clinical Events

6.9.1 Elritercept

6.9.1.1 Hypertension

During treatment with elritercept, participants may experience an increase in blood pressure. Thus, participants with uncontrolled hypertension will be excluded from the trial. For participants with hypertension who are eligible to enter the trial, hypertension will be controlled prior to treatment initiation and during treatment according to local practice and/or guidelines for the management of participants with hypertension. Blood pressure should be monitored prior to administration of each dose of trial intervention in accordance with the trial protocol. Anti-hypertensive agents should be used to manage new-onset hypertension or exacerbations of preexisting hypertension. There are no restrictions on anti-hypertensive medication use. Dose modification measures for participants experiencing Grade ≥ 3 hypertension, including dose delay and/or dose reduction, will be utilized to manage the risk.

6.9.1.2 ADA

As with all biologics, there is a potential risk of ADA with elritercept administration, which can be associated with increased drug clearance and hypersensitivity reactions. ADA assessment will be performed as indicated in the SoA. If a participant experiences a hypersensitivity reaction, injection site reaction, anaphylactic reaction, or other qualifying events, at the discretion of the investigator, a sample for measurement of ADA will be collected as soon as possible after the reaction is noted. Elritercept will be discontinued in participants experiencing Grade ≥ 3 related hypersensitivity reactions. ADA data will be routinely reviewed by the DMC, who will provide recommendations for action in specific cases of safety concerns.

6.9.2 Epoetin alfa

6.9.2.1 Hypertension

Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred during epoetin alfa treatment in patients with previously normal or low blood pressure. Participants with uncontrolled hypertension will be excluded from the trial. Participants with hypertension who are eligible to enter the trial,

CONFIDENTIAL

hypertension will be controlled prior to treatment initiation and during treatment according to local practice and/or guidelines for the management of participants with hypertension.

6.9.2.2 *Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism*

Using ESAs to target a Hgb level of >11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. For participants with a predose Hgb of ≥ 12.0 g/dL (7.5 mmol/L), dosing of epoetin alfa will be delayed until Hgb <11.0 g/dL (6.8 mmol/L). Patients with a high risk of cardiovascular diseases, stroke, and thromboembolism are excluded from trial participation.

6.9.2.3 *Increased Mortality and/ or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer*

Participants with a prior history of malignancies other than MDS, unless the participant has been free of the disease for ≥ 3 years, are not eligible for trial participation. During the trial, participants will be assessed for MDS disease progression every 24 weeks.

6.9.2.4 *Seizures*

Epoetin alfa should be used with caution in patients with epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity such as central nervous system infections and brain metastases. Patients with new-onset seizures or poorly controlled seizures within 12 weeks prior to randomization are excluded from trial participation.

6.9.2.5 *Rise in Platelet Counts*

During treatment with epoetin alfa, the platelet count may rise moderately dose-dependently within the normal range. This regresses during continued therapy. In addition, thrombocythemia above the normal range has been reported. The platelet count will be monitored regularly during the treatment.

6.9.2.6 *Serious Allergic Reactions*

Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur. The needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause severe allergic reactions in individuals sensitive to latex. In the event of serious allergic reactions, epoetin alfa will be discontinued immediately, and appropriate therapy will be administered.

6.9.2.7 *Severe Cutaneous Reactions*

Blistering and skin exfoliation reactions including erythema multiforme and Stevens-Johnson syndrome /toxic epidermal necrolysis, have been reported. Epoetin alfa will be discontinued, and reactions will be managed according to the local guidelines and or recommendations.

6.9.2.8 *Other Frequently Reported Adverse Reactions*

Other frequently reported adverse reactions in $\geq 5\%$ of epoetin alfa-treated patients in clinical trials are nausea, vomiting, myalgia, arthralgia, stomatitis, cough, weight decrease, leukopenia, bone pain, rash, hyperglycemia, insomnia, headache, depression, dysphagia, and hypokalemia. These AEs will be managed in accordance with the local practice and/or guidelines/recommendations.

Participant safety will be monitored closely through AE reporting, clinical laboratory tests, vital signs, and physical examinations.

7.0 **DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT WITHDRAWAL FROM TRIAL**

7.1 **Discontinuation of Trial Intervention**

7.1.1 **Criteria for Permanent Discontinuation of Trial Intervention**

The individual participant is considered to have discontinued trial intervention when the investigator determines no further trial intervention will be provided, or the participant withdraws consent, has died, is declared lost to follow-up or the sponsor terminates trial intervention.

EOTx is defined as the visit within 7 days after the decision to discontinue treatment is made and is intended to collect the protocol specified assessments. If the decision to discontinue trial intervention is made at a scheduled visit during the trial per the SoA, that visit should be considered the EOTx visit and all required assessments should be collected.

Discontinuation reported as due to noncompliance or protocol deviation to be discussed with medical monitor and confirmed with sponsor.

Trial intervention must be permanently discontinued for participants meeting any of the following criteria (See also [Table 6.d](#) and [Table 6.e](#)):

- Pregnancy (see Section [8.5](#)).
- Any Grade ≥ 3 suspected treatment-related injection site reaction, allergic reaction, anaphylaxis, or other hypersensitivity reaction.
- Any non-hematologic suspected treatment-related Grade 4 AE.
- Dose delay exceeding 90 consecutive days (except if due to an elevated Hgb level or platelet count).
- >2 dose reductions due to suspected treatment-related AE for epoetin alfa.
- Need for further dose reductions of elritercept below 2.5mg/kg for suspected treatment-related AEs.

- Need for further dose reductions of epoetin alfa below 337.5 IU/Kg for suspected treatment-related AEs.
- Severe cutaneous adverse reactions including Erythema multiforme and Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis is suspected in patients receiving epoetin alfa.
- PRCA is diagnosed in patients receiving epoetin alfa.
- Need for ongoing use of prohibited medication (See Section 6.8).

Treatment with trial intervention may also be discontinued for any of the following reasons:

- AE.
- Progressive disease:
 - Progression (See Table 16.g).
 - AML (WHO 2016).
- Unsatisfactory therapeutic response.
- Withdrawal by participant.
- Lost to follow-up.
- Protocol deviation.
- Trial terminated by sponsor (Refer to Section 4.3 for information on posttrial access).
- Other.

Once trial intervention has been discontinued, all procedures outlined for the end-of-treatment visit will be completed as specified in the SoA. The primary reason for trial intervention discontinuation will be recorded on the eCRF.

7.1.2 Temporary Discontinuation or Interruption of Trial Intervention

7.1.2.1 *Elritercept*

Dosing interruption may be required due to increased Hgb, increased platelet count, or TEAEs (Table 6.b). Trial visits and assessments should be conducted during dose delays as described in Section 8.2.5.

Participants who had a dose delay may resume dosing as soon as dosing criteria are met (Table 6.b).

If a participant experiences a treatment gap >90 days, trial intervention must be permanently discontinued, unless the treatment gap was due to an elevated Hgb or platelet count.

7.1.2.2 *Epoetin Alfa*

Dosing interruption may be required due to increased Hgb, increased platelet count, or TEAEs (Table 6.d). Trial visits and assessments should be conducted during dose delays as described in Section 8.2.5.

Participants who had a dose delay may resume dosing as soon as dosing criteria are met (Table 6.d).

If a participant experiences a treatment gap >90 days, trial intervention must be permanently discontinued, unless the treatment gap was due to an elevated Hgb or platelet count.

7.1.3 **Rechallenge**

Not applicable.

7.2 **Participant Withdrawal From the Trial**

Participants may withdraw themselves from the trial at any time and for any reason without prejudice to their future medical care by the physician or at the institution. The investigator is encouraged to discuss withdrawal of a participant with the medical monitor when possible.

Alternatively, participants may be withdrawn at any time during the trial at the discretion of the investigator or sponsor when the participant meets the trial termination criteria described in Section 10.5.

At the time of discontinuing from the trial, an end of trial eCRF will be completed.

The primary reason for withdrawal from the trial must be recorded by the investigator and reported in the eCRF.

A participant may be withdrawn from the trial for one of the following reasons:

- Lost to follow-up.
- Trial terminated by sponsor.
- Withdrawal by participant.
- Death.
- Other.

Following the date of participant withdrawal from the trial no additional assessments or information will be collected from the participant and added into the eCRF or any trial database.

See SoA (Section 1.3) and Section 8.2.6 for data to be collected at the EOTx visit and follow-up and for any further evaluations that need to be completed.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to attend scheduled visits and is unable to be contacted by the site.

The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

The site investigator or designee must make multiple attempts to contact the participant to request and reschedule the missed visits or treatment administrations as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the trial.

Before a participant is deemed lost to follow-up, the investigator or designee must document the multiple attempts to regain contact with the participant using multiple different means including if necessary, a certified letter to the participant's last known mailing address or local equivalent methods. These contact attempts should be documented in the participant's trial-specific record.

If the investigator or designee determines that the participant is deemed lost to follow-up then the participant will be considered to have withdrawn from the trial and document in the eCRF as per Section 7.2. After a participant is deemed lost to follow-up, the sponsor may consult public databases, if permitted in a given country, to determine survival status.

7.4 Trial Stopping Rules

One interim analysis will be conducted when approximately 110 enrolled participants have completed 24 weeks of treatment or discontinued treatment before reaching 24 weeks. If the DMC confirms futility based on interim analysis trial results, then the trial may be considered for termination.

At the primary analysis, if the superiority test on the primary endpoint fails, the trial will be terminated.

In addition, the DMC may consider recommendation for termination of the trial due to safety concerns.

8.0 TRIAL ASSESSMENTS AND PROCEDURES

8.1 Screening/Baseline Assessments and Procedures

Before trial assessments and procedures can be performed, informed consent must be obtained (signed and dated), as described in Section 10.3.

Screening assessments are to be completed within 6 weeks (42 days) prior to randomization. This period may be extended by 2 weeks for a total of 8 weeks to complete transfusion history if needed and/or up to an additional 6 weeks for central pathology review of bone marrow for eligibility if discussed with the medical monitor.

Safety laboratory assessments should be collected within 14 days before randomization. When multiple results are available, the most recent evaluable central result(s) will be used to determine eligibility. Other assessments may be performed throughout the screening period at the investigator's discretion; however, these assessments must be completed and results obtained before randomization.

If evaluable central laboratory results are not available for safety laboratory assessments, the participant may not be randomized. Of note, local results may be used to determine eligibility only in exceptional circumstances and when pre-approved by the medical monitor.

8.1.1 Demographics, Medical History, and Medication History

8.1.1.1 Demographics

Participant demographic information (the year of birth, race, ethnicity, sex) will be collected during the screening phase, as local laws permit.

8.1.1.2 Medical History

Medical and medication history, including concurrent medical conditions and recent surgical history, will be collected, and recorded in the participant's source documents and in the eCRF.

This should include relevant information related to MDS diagnosis (including date of original diagnosis, WHO at the time of diagnosis, signs/symptoms, prior therapies administered for MDS) and/or other past malignancies.

Medical history to be obtained will include determining whether the participant has any significant conditions or diseases relevant to the disease under trial that were resolved within the screening period prior to signing the ICF by the participant. Ongoing conditions are considered concurrent medical conditions.

Concurrent medical conditions are those significant ongoing conditions or diseases that are present when informed consent is provided. This may include clinically significant laboratory, ECG, physical examination, and/or vital signs abnormalities noted at screening, according to the judgment of the investigator. The condition (that is, diagnosis) should be described.

History of platelet transfusions to be provided if received in the past 8 weeks.

8.1.1.3 Transfusion History

Comprehensive reporting of all RBC and platelet transfusions administered during the 8 weeks preceding the planned enrollment (for example, randomization) must be collected and recorded in the participant's source document.

For each platelet transfusion event, report the following information in the eCRF for the Screening visit or alternative documentation as permitted by sponsor:

- Date of platelet transfusion.

- Number of units.
- Indication.
- Pretransfusion platelet (within 7 days) date of sample and value.

For each RBC transfusion event, report the following information in the eCRF for the Screening visit or alternative documentation as permitted by sponsor:

- Date of RBC transfusion.
- Number of pRBC units.
- Indication.
- Presence of symptomatic anemia.
- Pre-transfusion Hgb (within 3 days) date of sample and value.

Evaluable transfusion events:

- Hgb levels no more than 3 days prior to administration of a RBC transfusion must have been ≤ 9.0 g/dL (5.6 mmol/L) with symptoms of anemia or ≤ 7 g/dL (4.3 mmol/L) in the absence of symptoms for the transfusion to be counted as an evaluable transfusion event towards meeting eligibility criteria and stratification as HTB or LTB.
- RBC transfusions administered when Hgb levels were >9.0 g/dL or >7 g/dL in the absence of symptoms, and/or RBC transfusions administered for elective surgery, infections or bleeding events will not qualify as an evaluable transfusion event for the purpose of meeting eligibility criteria or transfusion burden stratification.

Only RBC transfusions given for anemia related to MDS will be counted as evaluable transfusion events for assessment of transfusion burden during eligibility assessment and used for stratification. Transfusions for intercurrent diseases (bleeding, surgical procedure, infection, and so on.) will not be considered evaluable transfusion event. In addition, RBC transfusion given with pretransfusion Hgb levels >9 g/dL will not be counted as an evaluable transfusion event, but all transfusions should be recorded.

Baseline transfusion requirements will impact randomization stratification (LTB versus HTB) and errors in stratification may impact balance between trial arms. To mitigate this risk, participants with LTB will be evaluated for anticipated transfusion needs before randomization. If a participant is anticipated to need a transfusion between randomization and C1D1, which would change their classification from LTB to HTB, it may be required to delay randomization and extend the Screening Period until baseline transfusion requirements are stable and stratification factors can be accurately assigned.

Furthermore, baseline RBC transfusion and corresponding hematology data will be evaluated by the medical monitor before randomization.

8.1.1.4 *Prior and Concomitant Medications*

At the time of the medical history, any available prior medication information will be collected.

Prior and concomitant medications will be collected and recorded in the participant's source document and eCRF.

Such medications include but are not limited to:

- Medications or vaccines.
- Over-the-counter or prescription medicines.
- Recreational drugs.
- Vitamins.
- Herbal supplements.
- Medications relevant to the eligibility criteria.
- Iron chelation therapy.
- Any therapies received for MDS must be reviewed with medical monitor to confirm eligibility as outlined in the exclusion criteria.

Prior medications are defined as those that were:

- Any medications taken for MDS prior to signing to ICF.
- Being taken at the time of signing the ICF.
- Stopped at or within 30 days before signing the ICF.

Concomitant medications are defined as those given in addition to the trial intervention:

- Between the signing of the ICF and end of safety follow up (60 days after last dose).

Concomitant medications may be prescribed by a physician or obtained by the participant over the counter, apart from those listed in the Prohibited Concomitant medication section.

Concomitant medication is not provided by the sponsor.

At each trial visit, participants will be asked whether they have taken any medication or received any treatment other than the trial intervention.

The following information will be recorded: the reason/indication for use, dates of administration, dates of discontinuation, and dosage information.

RBC transfusion data will be collected as per Section [8.2.3](#).

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

8.1.1.5 Concomitant Procedures

If the participant receives any diagnostic or therapeutic procedures and/or any MDS-associated therapies including platelet transfusion during the treatment period between C1D1 and EOTx, record in the eCRF designated procedures form. Record name of procedure, date, indication and as applicable any outcome.

Note administration of growth factors for MDS-associated symptom management to be reported on the concomitant medications.

8.1.1.6 Diagnostic Criteria/Disease Classification

Confirmation of MDS disease diagnosis and IPSS-R categorization using WHO 2016 and IPSS-R ([Greenberg et al. 2012](#)) criteria is performed by an independent central reviewer during Screening. Samples including bone marrow aspirate, bone marrow core biopsy, and blood must be collected within the first week of the Screening Period and submitted to a central pathology laboratory to allow sufficient time for confirmation of diagnosis, RS status, and IPSS-R score within 6 weeks of the planned date of randomization.

If appropriate and agreed upon by the sponsor, local test results may be used as part of IPSS-R scoring.

Bone marrow biopsy, bone marrow aspirate, and peripheral blood samples will be collectively assessed for cellular composition (including cellularity and blast percentage), morphology and dysplasia (including RS status), cytogenetics (including karyotype and FISH), and MDS-relevant somatic mutations. The assessment of morphology and dysplasia should be performed on peripheral blood as well as bone marrow.

For diagnosis of MDS, required procedures include bone marrow aspirate, bone marrow core biopsy, and peripheral blood collection.

- Bone marrow aspirate and core biopsy; samples should be collected at least 14 days after RBC transfusion or 7 days after platelet transfusion.
- Blood samples for peripheral blood smears should be collected on the same day as the bone marrow samples and submitted to central pathology laboratory.
- Blood samples for hematology parameters (Hgb, neutrophils, platelets) may be collected on date of bone marrow sample but must be collected at least 14 days following an RBC transfusion or at least 7 days following a platelet transfusion to be used to evaluate IPSS-R for eligibility, unless reviewed with the medical monitor and the investigator to confirm if the collection is considered to be pretransfusion. The sample is to be submitted and reported by central laboratory (local laboratory results may be used if unable to retrieve samples or results for central laboratory within the specified collection timepoint).

8.1.1.7 *Coagulation Panel*

Coagulation evaluation will be performed at screening only and submitted to central laboratory. The coagulation panel includes aPTT, prothrombin time, and INR. Additional coagulation samples may be collected as clinically indicated.

8.2 **Efficacy Assessments and Procedures**

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3). All trial visits should be scheduled based upon first dose of trial intervention (C1D1).

8.2.1 **Pretransfusion Assessments**

Transfusions are expected to impact multiple assessments in this trial. As such, collection of pretransfusion blood samples is essential for meeting trial objectives. If a participant is to receive a transfusion on the day of dosing, the transfusion must be completed prior to dosing.

8.2.1.1 *Baseline Hgb Threshold for RBC Transfusions*

Baseline Hgb threshold is the mean value of all evaluable Hgb values (See Section 17.2) during the 8 weeks prior to randomization. This baseline Hgb threshold will be provided to the investigator for each participant and this value will be used throughout the treatment period for assessment of transfusion requirement.

During the treatment period at the time of the next anticipated RBC transfusion event, if the pretransfusion Hgb level is increased by ≥ 1.0 g/dL (0.6 mmol/L) compared to the baseline Hgb threshold, the RBC transfusion should be delayed by a minimum of 7 days. Participants may be transfused at the investigator's discretion for symptoms related to anemia or other requirements (such as, infection).

8.2.1.2 *Pretransfusion Assessments for RBC Transfusions*

Any time a participant requires an RBC transfusion, pretransfusion blood sample should be collected ≤ 3 days prior to transfusion and analyzed for hematology (CBC with differential) to confirm Hgb level. If a posttransfusion Hgb level is collected, it should be recorded (unscheduled). In addition, pretransfusion blood sample should be collected prior to transfusion and analyzed for ferritin, TSAT, NTBI, and serum EPO to monitor for iron overload.

8.2.1.3 *Pretransfusion Assessments for Platelet Transfusions*

For any platelet transfusion received during the trial, a pretransfusion blood sample should be collected ≤ 3 days prior to the transfusion and analyzed for hematology (CBC with differential) to confirm platelet level. If a posttransfusion platelet level is collected, it should be recorded (unscheduled).

8.2.2 Transfusion Verification

Comprehensive data collection of all RBC and platelet transfusions will be recorded in the eCRF after first dose until the next transfusion date after EOTx. If the participant had an EOTx visit before 24 weeks, continue to record transfusion data through 24 weeks; if no transfusions were reported between EOTx and 24 weeks, then monitor until the next transfusion date. For participants continuing on trial intervention after 24 weeks, continue to collect comprehensive transfusion data until next transfusion date after the EOTx Visit.

The following information will be collected for comprehensive verification of RBC transfusions and reported in the eCRF:

- Date of transfusion (and time if known), type (pRBC or platelet) number of pRBC or platelet units, and indication.
- Pretransfusion Hgb and platelet (≤ 3 days) collection date (and time if known) and value (may include local laboratory values if central laboratory values are not available during the screening and treatment period).

If a participant receives a RBC transfusion at the trial site a pre-transfusion Hgb must be collected within 3 days prior to the transfusion, and the clinical site-designated staff must document the RBC transfusion data including pre-transfusion Hgb in the participant's source record (primary source documentation).

If a participant receives a RBC transfusion at institutions outside of the trial site in between trial visits, the clinical site-designated staff should request copy of primary source documentation from the other institution, or a copy of a physician report stating the transfusion was received including date, number of units and pre-transfusion Hgb (secondary source documentation).

All RBC transfusion events for any indication (that is, anemia, elective surgery, infections or bleeding events) must be recorded in the eCRF.

8.2.3 MDS Disease Assessment

MDS Disease Assessment must be performed by the investigator during the Treatment Period after the participant completes 24 weeks and 48 weeks of treatment, and then as clinically indicated until the EOTx. EOTx MDS Assessment is required if >6 months since prior collection, as indicated in the SoA (Section 1.3).

Unscheduled MDS Disease Assessments may also occur (Section 1.3) as clinically indicated at the discretion of the investigator. Bone marrow samples (or portion thereof) should be submitted to central pathology laboratory to report results or if not available then report local laboratory results or if not available then report local laboratory results to be record as unscheduled visits.

A ± 14 -day window is allowed for MDS Disease Assessment procedures during the treatment period. It is reasonable to expect that central pathology laboratory results from MDS Disease Assessment procedures will be available approximately 4 weeks after collection. The every-24-week schedule for the MDS Disease Assessment should be calculated from C1D1, regardless of dosing cycles. The MDS Disease Assessment may or may not align with scheduled

visits (for example, C7D1, C13D1, and so on) if the participant has been dose delayed due to AEs and/or dose-modification criteria specified in Sections 6.3.1 and 7.1.2.

At 24 calendar weeks after C1D1, if central pathology results required for the MDS Disease Assessment are not available at the time of the next dosing visit, participants may complete that visit (including dosing) as scheduled; however, the MDS Disease Assessment must be completed as soon as central pathology results are available and within 6 weeks of the bone marrow collection.

MDS Disease Assessment procedures include bone marrow aspirate, bone marrow core biopsy, and peripheral blood collection.

- Bone marrow aspirate procedures should be scheduled more than 14 days after RBC or platelet transfusion; Bone marrow core biopsy is optional at Week 49 (Cycle 13) MDS Assessment.
- Blood samples for peripheral blood smears should be collected on the same day as the bone marrow is submitted to central pathology laboratory.
- Blood samples for hematology parameters (Hgb, neutrophils, platelets) should be collected on date of bone marrow but must be collected at least 14 days following an RBC transfusion or at least 7 days following a platelet transfusion unless reviewed by medical monitor and the investigator to confirm if the collection is considered to be pretransfusion. The sample to be submitted and reported by central laboratory (local laboratory results may be used if unable to retrieve samples for central laboratory within the specified collection timepoint).

Importantly, if the participant requires an RBC or platelet transfusion on the same day as the bone marrow procedure, the peripheral blood sample should be collected before the transfusion is administered to ensure that it is not impacted by RBC or platelet transfusion.

Refer to the Laboratory Manual for additional details on sample collection, storage, and analysis of bone marrow and peripheral blood samples for the MDS Disease Assessment.

With each MDS Disease Assessment, the response assessment will be based on central pathology laboratory results reviewed by the Investigator. Record in eCRF any progressive disease status, including high and higher-risk MDS (Higher-risk MDS; HR-MDS per IPSS-R), myeloproliferation (for example clinically significant increases in blasts) or AML.

After Week 49 (Cycle 13), report MDS Disease Assessment every 6 months based on clinical assessment of available hematology and transfusion requirement, and as indicated any bone marrow assessment.

The SoA (Section 1.3) specifies details about the timing of efficacy assessments and associated sampling and assessments.

8.2.4 HRQoL Measures

Participants will be asked to complete the following PRO measures electronically at designated trial visits:

- EORTC QLQ-C30,
- FACT-An Anemia scale,
- the EQ-5D-5L,
- a transfusion burden assessment, and
- PGI-S and PGI-C items for fatigue, anemia symptoms, and physical function.

The EORTC QLQ-C30, FACT-An Anemia scale, and PGI-S items should be completed at screening, Day 1 of Cycle 1 and Day 1 of each subsequent cycle, and at EOTx. The EQ-5D-5L and transfusion burden assessment should be completed at each of the same time points except screening, while the PGI-C items should be administered at the same time points as the EQ-5D-5L and transfusion burden assessment except screening and Day 1 of Cycle 1.

Participants who discontinue treatment during the 24 weeks following first dose should return to the trial site at fixed time points to complete the battery of PRO measures. In addition, the EQ-5D-5L should be completed electronically at the two safety visits and by telephone interview at survival contacts occurring quarterly from the time of last dose. The collection of EQ-5D-5L data following treatment discontinuation is intended to support market access and health technology assessment needs. Further details on the administration of the PRO measures are provided in [Table 1.c](#) and [Table 1.d](#).

The questionnaires are intended to be completed in the following order:

1. EORTC QLQ-C30
2. FACT-An Anemia scale
3. EQ-5D-5L
4. Transfusion burden assessment
5. PGI-S/PGI-C fatigue
6. PGI-S/PGI-C anemia symptoms
7. PGI-S/PGI-C physical function

When possible, participants should complete the questionnaires prior to any other assessments or trial procedures. If a participant is unable to complete one or more questionnaires, the reason for this should be documented. The questionnaires should be provided in the participant's preferred language if available. If exceptional circumstances preclude the continued administration of questionnaires using the planned electronic or telephonic modality, then alternate administration methods may be required after consultation with the sponsor or the sponsor's representative.

8.2.4.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a 30-item, patient-reported multidomain questionnaire designed to assess the functioning, well-being, and symptom experience of patients with cancer ([Aronson et al. 1993](#)). The questionnaire's items are divided among 5 multi-item scales measuring functioning (physical, role, emotional, cognitive, and social), 3 multi-item scales measuring symptoms (fatigue, nausea/vomiting, and pain), 6 items measuring symptoms (dyspnea, insomnia, appetite loss, constipation, and diarrhea) as well as financial difficulties, and a 2-item scale measuring global health status and QoL. Items included in the global health status/QoL scale utilize a 7-point response metric ranging from *Very Poor* to *Excellent*, while other items use a 4-point response metric with categories including *Not at all*, *A little*, *Quite a bit*, and *Very much*. Scale scores are transformed to range from 0 to 100 with higher scores indicating better functioning, better health status/QoL, or worse symptomatology. The questionnaire uses a recall period of 1 week.

The EORTC QLQ-C30 is among the most widely used PRO measures in clinical trials of patients treated for MDS ([Giesinger et al. 2021](#); [Stauder et al. 2020](#)) and has been validated for use in MDS and other hematologic malignancies ([Efficace et al. 2023](#); [Efficace et al. 2019](#); [Efficace et al. 2018](#); [Lewis et al. 2024](#); [Lyons et al. 2023](#); [Regnault et al. 2021](#)). For group-level analyses, clinically meaningful changes in EORTC QLQ-C30 scale scores can be defined using thresholds ([Cocks et al. 2012](#)). For participant-level analyses, meaningful changes in scale scores can be defined using responder definitions ([Cocks and Buchanan 2023](#)).

8.2.4.2 FACT-An Anemia Scale

The FACT-An questionnaire is used to assess the effects of disease symptoms on functioning and well-being in patients with anemia ([Cella 1997](#)). The questionnaire includes a core consisting of the 27-item FACT-General ([Cella et al. 1993](#)) as well as a 20-item Anemia scale. To limit redundancy with other PRO measures, only the Anemia scale will be administered in this trial. The FACT-An Anemia scale includes 13 fatigue-specific items (which together comprise the FACIT-Fatigue scale) in addition to 7 items specific to anemia but unrelated to fatigue. The Anemia scale's items use a 5-point response metric ranging from *Not at All* to *Very Much*. Item responses are summed to produce a score ranging from 0 to 80 (with scores for the embedded FACIT-Fatigue scale ranging from 0 to 52). The Anemia scale uses a recall period of 1 week. Meaningful within-patient changes in scores for the FACT-An Anemia scale and FACIT-Fatigue scale have been reported as 4 points and 3 points, respectively ([Cella et al. 2002](#)). The validity and reliability of the Anemia scale (including the FACIT-Fatigue scale) have been demonstrated in MDS patient populations ([Brandenburg et al. 2010](#); [Castelli et al. 2014](#); [Revicki et al. 2013](#); [Ryblom et al. 2015](#); [Spiriti et al. 2005](#); [Trudeau et al. 2020](#)).

8.2.4.3 EQ-5D-5L

Participants' reports of general health status will be assessed using the EQ-5D-5L questionnaire ([Herdman et al. 2011](#)). The EQ-5D-5L has 2 components: a descriptive system and a VAS. The

instrument's descriptive system consists of 5 items measuring problems with mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents are asked to classify problems in each dimension as *no*, *slight*, *moderate*, *severe*, or *extreme* or *unable to*. A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 5. Thus, the numbers 11111 and 55555 represent the best health state and the worst health state, respectively, described by the EQ-5D-5L. Altogether, the instrument describes $5^5 = 3,125$ health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D-5L to generate a utility index measuring the value to society of his or her current health. In addition, the VAS allows respondents to rate their own current health on a 101-point scale ranging from 0 = *worst imaginable* to 100 = *best imaginable*. The EQ-5D-5L uses a recall period of *TODAY*.

The EQ-5D has been used in MDS clinical trials ([Giesinger et al. 2021](#)), ([Stauder et al. 2020](#)) and has been shown to be predictive of outcomes in patients treated for MDS ([Pleyer et al. 2023](#)). Among patients with cancer, meaningful changes in EQ-5D VAS scores and utility index scores have been estimated at 5-7 points and 0.03-0.08 points, respectively ([Bourke et al. 2024](#); [Pickard et al. 2007](#)).

8.2.4.4 Transfusion Burden Assessment

A single item measuring the participant-perceived burden of red blood cell transfusions (including time commitment as well as physical and emotional burden) will be administered in the trial. The item will use a 5-point response metric ranging from *Not At All* to *Extremely* and a 4-week recall period.

8.2.4.5 PGI-S/PGI-C Items

To facilitate the validation of thresholds for meaningful within-patient changes in HRQoL outcomes, single items measuring participant perceptions of severity and change will be administered in the trial. Distinct sets of PGI-S and PGI-C items will be administered for fatigue, anemia symptoms, and physical function, yielding a total of 6 items. The items will use 5-point response metrics with categories including *No*, *Mild*, *Moderate*, *Severe*, and *Very Severe* for PGI-S items and *Much Better*, *A Little Better*, *No Change*, *A Little Worse*, and *Much Worse* for PGI-C items. The PGI-S items will ask participants to rate the severity of symptoms or functional limitations over the preceding week, while PGI-C items request participants to evaluate changes in outcomes since the start of trial intervention.

8.2.5 Trial Assessments During Dose Delays

If trial intervention is not administered on a Day 1 visit (Section [6.3.1](#) and [6.3.2](#)), the planned assessments for that day should be collected as outlined in the SoA (Section [1.3](#)). Refer to guidelines for data entry. Additional assessments to be collected at the discretion of the Investigator, in consultation with the medical monitor as needed, to monitor the participant status.

During dose delay, assessments to include but not limited to the following:

CONFIDENTIAL

- Hematology sample on Day 1 visit and every 2 weeks, and additionally as per investigator discretion.
- Chemistry sample if on Day 1 and every 4 weeks, and additionally as per investigator discretion.
- Serum epoetin sample if on Day 1 visit and every 4 weeks.
- ADA sample if on Day 1 and every 4 weeks.
- PROs if on Day 1 and every 4 weeks.

On day dosing resumes, before administration of trial intervention all Day 1 assessments to be collected with the following exception if completed within 14 days prior:

- Weight.
- Pregnancy testing.
- ECG or echocardiogram.
- Serum for circulating biomarkers.

Additional visits outside of the scheduled visits detailed in the SoA (Section 1.3) are to be recorded as unscheduled visits.

Elritercept:

When the elritercept dosing is permitted to resume record the dose as Day 1 of the next cycle following the previous dose received. Refer to guidelines provided separately on how to document when dosing resumes.

Epoetin alfa:

If a cycle has started and a dose is delayed, record the data within that cycle but if the cycle has not started then record the data in Unscheduled visits until dosing resumes. Refer to guidelines provided separately on how to document when dosing resumes.

8.2.6 Posttreatment Follow-Up

8.2.6.1 Safety Follow-Up

Participants will be monitored for safety for a minimum of 60 days after last dose of trial intervention. If a positive ADA is reported, then collect ADA samples quarterly for additional ADA testing until a negative result is obtained or until 12 months post-EOTx, whichever is earlier (See Table 1.d).

Investigators should report all AEs and concomitant medications during this time period regardless of causality. Record any subsequent treatment for MDS initiated after EOTx.

EQ-5D-5L should be completed electronically at the two safety visits.

8.2.6.2 *Survival Follow-Up*

Participants will enter a survival follow-up period after the EOTx visit for up to 5 years from randomization as specified in Section 1.3 or until lost to follow-up, consent withdrawal, death, or trial termination by sponsor, whichever occurs first. Report the survival status. The preferred method of contact during the survival follow-up period is by telephone. If unable to reach the participant by telephone, other methods to assess status may be used, including but not limited to, email, mail, or soliciting status from online or other public databases (for example, Social Security indexes).

EQ-5D-5L should be completed by telephone interview at survival contacts occurring quarterly from the time of last dose.

Report any subsequent treatments for the disease under trial including onset date, name of treatment, and if known, dose, frequency, and end date. The following are exceptions to collecting subsequent therapy.

- After EOTx report date of next RBC transfusion including date and units received recorded on the eCRF form for collection of transfusion data; report RBC transfusion until Week 24 as described in Section 8.2.1.
- After EOTx report date of next platelet transfusion and/or iron chelation treatment once.

Any progressive disease changes are to be reported, including high and higher-risk MDS (Higher-risk MDS; HR-MDS per IPSS-R), myeloproliferation (for example, clinically significant increases in blasts), or AML. Survival status to be reported and in case of death the date of death and primary cause of death are to be reported.

The EOTx visit serves as the early termination visit, as applicable.

8.3 **Safety Assessments and Procedures**

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 **Physical Examination**

A physical examination will be completed per standard of care at the times specified in the SoA (Section 1.3).

8.3.2 **Vital Signs**

Vital signs will be completed at the times specified in the SoA (Section 1.3). Vital sign measurements include sitting diastolic and systolic blood pressure after resting for more than 5 minutes, heart rate, respiratory rate, and body temperature.

Blood pressure and pulse measurements will be assessed after 5 minutes rest in a quiet setting without distractions (for example, television, cell phones) while seated comfortably, both feet flat on the floor and back supported. Blood pressure should be determined by cuff with an automated device. Manual techniques will be used only if an automated device is not available.

Three readings of blood pressure and pulse will be performed (approximately 5 minutes apart) and all 3 values should be recorded, and the mean value.

The mean value will be used to evaluate dose modifications.

Circumstances in which a change in vital signs would be reportable as an AE:

The investigator will assess whether a change in vital signs from baseline until the end of safety follow-up may be deemed clinically significant on the Vital Signs eCRF and whether the change should be considered and recorded as an AE on the AE eCRF.

8.3.2.1 Weight and Height

A participant should have weight and height measured while wearing indoor clothing and with shoes off. Weight is collected in kg. Height is recorded in cm.

Height and weight will be captured per SoA (Section 1.3). Height will be measured only during screening. Weight will be assessed monthly during treatment period and as stated in Section 6.3.

8.3.3 ECGs and Echocardiograms

8.3.3.1 ECGs

A 12-lead ECG will be performed locally at the trial site at the time points specified in the SoA. ECGs will be reviewed locally by the investigator. The following ECG parameters will be recorded on the respective eCRF(s): for example, heart rate, PR interval, QRS duration, and QT interval.

The investigator (or a qualified designee) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. Clinically significant abnormal findings will be reported as AEs and the investigator may consult a cardiologist if deemed appropriate.

8.3.3.2 Echocardiogram

An echocardiogram will be performed at the timepoints specified in the SoA. Report LVEF and if available, collect STRAIN echocardiogram with low left ventricular global longitudinal strain results.

Clinically significant abnormal findings will be reported as AEs, and the investigator may consult a cardiologist if deemed appropriate.

8.3.4 Clinical Laboratory Assessments

8.3.4.1 Use of Local Versus Central Laboratories

All hematology, chemistry, and urine samples collected for safety assessment and disease assessment are to be submitted to the central laboratory. During treatment period, samples to be collected per SoA (Section 1.3). Additional hematology samples are to be collected ≤ 3 days prior

to any transfusion and as clinically indicated for safety evaluation. These additional samples should be sent to the central laboratory. If samples are unable to be retrieved for central laboratory analysis, then local laboratory results must be collected and reported in the eCRFs.

Handling and shipment of clinical laboratory samples will be outlined in the Laboratory Manual.

8.3.4.2 Clinical Hematology

Blood samples for analysis of the clinical hematology parameters shown in [Table 8.a](#) will be obtained as specified in the SoA (Section [1.3](#)).

Table 8.a Clinical Hematology Tests

Hematology
Hematocrit
Hgb
WBC; count
Leukocytes with differential (% and absolute)
Neutrophils
Eosinophils
Basophils
Lymphocyte
Monocytes
ANC; count
Platelet (count)
Red blood cell (count)
Reticulocyte count (% and absolute)
Reticulocyte hemoglobin
Reticulocyte production index
Mean corpuscular volume
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean platelet volume
Blasts (%)
Albumin
ALP
ALT
AST
Bilirubin (total)
Blood urea nitrogen (BUN)
Calcium
CO ₂
Creatinine

Table 8.a Clinical Hematology Tests

Hematology
Creatine kinase sEPO

8.3.4.3 Clinical Chemistry and Urinalysis

Blood samples for analysis of chemistry parameters shown in [Table 8.b](#) and urine samples for analysis of the parameters shown in [Table 8.c](#) will be obtained as specified in the SoA (Section [1.3](#)).

Table 8.b Clinical Chemistry Tests

Serum Chemistry
Chloride Folate Gamma glutamyl transferase Glucose Lactate dehydrogenase Magnesium Phosphorus Potassium Total protein Sodium Uric acid Vitamin B12 Vitamin B6

Table 8.c Clinical Urinalysis Tests

Urinalysis	
Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood	pH Protein Specific gravity Turbidity and color Urobilinogen

8.3.5 Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

CONFIDENTIAL

8.4 AEs and SAEs

A quick reference for safety reporting is shown in [Table 8.d](#).

Table 8.d Safety Reporting Timeframes

Safety Event	How to Report Event to Safety	Reporting Timelines to Sponsor Time Since Awareness of Event
SAEs	Complete AE eCRF (If EDC is unavailable, submit paper SAE form)	Within 24 hours
Pregnancy	Complete and submit paper pregnancy form	24 hours
SSRs	Complete and submit paper SSR form	7 calendar days

8.4.1 Definitions of AE and SAE

8.4.1.1 AE Definition

An AE is any untoward medical occurrence in a clinical trial participant, temporally associated with the use of the trial intervention, whether or not the occurrence is considered related to the trial intervention.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the trial intervention.

An untoward finding generally may necessitate therapeutic intervention, require an invasive diagnostic procedure, or require discontinuation or a change in dose of trial intervention or a concomitant medication. (Repeated or additional noninvasive testing [such as, laboratory or ECG retests] for verification, evaluation, or monitoring of an abnormality is not considered a therapeutic intervention.)

Appendix [12.1](#) provides additional details and clarifications for regarding AEs.

8.4.1.2 SAE Definition

SAEs are events that meet BOTH the AE definition described in Section [8.4.1.1](#) and as amended in Section [12.1](#) AND the criteria for seriousness below.

An SAE is defined as any untoward medical occurrence that meets 1 or more of the criteria listed:

- a) Results in death.
- b) Is life threatening.

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

CONFIDENTIAL

- c) Requires inpatient hospitalization or prolongation of existing hospitalization.
- d) Results in persistent or significant disability/incapacity.
- e) Is a congenital anomaly/birth defect.
- f) Other situations (medically significant event):
 - Is an important medical event.
 - May require intervention to prevent one of the outcomes listed above.
 - May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
 - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
 - Is a suspected transmission of any infectious agent via an authorized medicinal product.
 - ALT/AST $\geq 3 \times \text{ULN}$ and total bilirubin $> 2 \times \text{ULN}$ or INR $> 1.5 \times \text{ULN}$ for which an alternative etiology has not been found. Please also contact the medical monitor and Takeda trial clinician within 24 hours.

Additional details and clarifications for SAEs are in Appendix [12.2](#).

8.4.2 Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from the signing of the ICF until 60 days after the administration of the last dose of elritercept or epoetin alfa at the time points specified in the SoA (Section [1.3](#)).

SAEs will be collected and reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed (e)consent through 60 days after administration of the last dose of elritercept or epoetin alfa and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es).

8.4.3 Identifying AEs and SAEs

The investigator and any qualified designees are responsible for identifying events that meet the definition of an AE or SAE.

AEs will be assessed at the frequency shown in the SoA using open questions asked of the participant/participant's caregiver, surrogate, or legally authorized representative by the investigator or trial personnel. AEs may also be spontaneously reported at any time or revealed

by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE.

8.4.4 Recording of AEs and SAEs

8.4.4.1 Recording of AEs

All AEs will be recorded on the appropriate page of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event. For both serious and nonserious AEs, the investigator must determine:

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, version 5.0 or higher. The criteria will be provided separately.

Relationship (that is, causality) of the event to trial intervention administration, will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the trial intervention? Please note that *trial intervention* includes all IMPs.

Outcome at the time of recording, assessed as recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, or unknown.

8.4.4.2 Recording of SAEs

All SAEs will be recorded immediately in the eCRF, within 24 hours of awareness.

AEs assessed as serious (SAEs) will trigger an SAE report and automatically transmit the report to Takeda Safety. If transmission of an EDC SAE report is not feasible, then an email or a facsimile of the completed Takeda paper-based SAE form must be sent. A sample of the paper-based SAE form and processing directions will be provided by the sponsor.

Once EDC becomes available, ensure the SAE is also recorded in the eCRF. Information in the SAE report or form must be consistent with the data provided on the eCRF.

Further details on assessing severity and causality of AEs and SAEs are in Appendices [12.3](#) and [12.4](#).

8.4.5 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts.

Regardless of causality, all AEs must be monitored until 60 days after the administration of the last dose of elritercept or epoetin alfa or until the participant is withdrawn (Section [7.2](#)) or lost to follow-up as defined in Section [7.3](#).

SAEs must be monitored until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

If information not available at the time of the first SAE report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (for example, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

8.4.6 Reporting of SAEs

Regardless of causality, SAEs must be reported by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event.

This will be done by transmitting an EDC SAE report. If transmission of an EDC SAE report is not feasible, then an email or facsimile of the completed Takeda paper-based SAE form will be sent (Email: PVsafetyoncologyAmer@takeda.com; Fax: +1-224-554-1052).

A sample of the paper-based SAE form and processing directions will be provided separately. Information in the SAE report or form must be consistent with the data provided on the eCRF.

Follow-up SAE reports will follow the same procedure and time course.

8.4.7 Regulatory Reporting Requirements for SAEs

All SAEs must be recorded and reported to the sponsor or designee immediately, via the procedure described in Section 8.4.4. Under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a trial intervention under clinical investigation are met. The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the elritercept IB and epoetin alfa package insert and will notify the IRB/IEC, if appropriate according to local requirements.

The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMP's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

8.4.8 Serious and Unexpected Adverse Reaction Reporting

The sponsor will be responsible for reporting all SUSARs to regulatory authorities, the EudraVigilance database, investigators, and IRBs and IECs, as applicable, in accordance with national regulations in the countries where the trial is conducted.

Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations.

8.4.9 AEs of Special Interest

Not applicable.

8.4.10 Disease-related Events or Outcomes Not Qualifying as AEs or SAEs

The following DREs are common in participants with MDS and can be serious:

- Planned hospital admissions or surgical procedures for an illness or disease that existed before the participant was enrolled in the trial or before trial intervention was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (for example, surgery was performed earlier or later than planned).
- Scheduled therapy for the target disease of the trial, including admissions for transfusion support or convenience, is not considered an SAE.

Note: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.
- The investigator considers that there is a reasonable possibility that the event was related to trial intervention.

8.4.11 Special Situations

Special situations may or may not be associated with an AE/SAE but are not, in and of themselves, AEs. If special situation results in an SAE, the SAE should be reported.

Individuals who identify a potential special situation should immediately report this via a paper Special Situation Report form within 7 calendar days to the contact information provided separately.

The following classes of special situations might occur:

Abuse – persistent or sporadic intentional excessive use of medicinal products accompanied by harmful physical or psychological effects.

Misuse – situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol-specified dose, route of administration, and/or indication.

Medication Error– An unintentional error in the drug treatment process (prescribing, dispensing or administration, including incorrect dose or poor-quality administration) of a medicinal product while in the control of trial site-designated staff or a participant that leads to harm or has the potential to lead to harm.

Overdose – the administration of a quantity of medicinal product given per administration or per day, which is above the maximal recommended dose according to the protocol. When applying this definition, clinical judgement should always be applied.

Pregnancy – See Section 8.5.

8.4.12 Product Complaints

A product complaint is a verbal written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. These could include suspicion that a trial intervention has been counterfeited.

Individuals who identify a potential product complaint situation should immediately report this via the contact information provided separately.

Product complaints and medication errors in and of themselves are not AEs. However, AEs or SAEs resulting from a product complaint should be reported.

8.5 Pregnancy and Postpartum Information

8.5.1 Participants Who Become Pregnant During the Trial

8.5.1.1 Reporting

Pregnancy in and of itself is not an AE, unless a negative or consequential outcome occurs in the participant or child/fetus. If the negative event meets the seriousness criteria, then this is considered an SAE (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy, or pre-eclampsia) and reported per Section 8.4.6, Reporting of SAEs.

Details about all pregnancies in participants or their partners will be collected from the signing of ICF and until 60 days after the last dose of the trial intervention. Collection of pregnancy data from a participant's partner requires the partner's informed consent.

Once a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours (Email: PVsafetyoncologyAmer@takeda.com; Fax: +1-224-554-1052).

To the extent possible, the investigator will collect follow-up information on the outcome of the pregnancy and the neonate, and the information will be forwarded to the sponsor.

8.5.1.2 *Continued Trial Participation*

Participants who suspect pregnancy while participating in this trial, must inform the investigator immediately and discontinue trial intervention until further notice. Any participant who becomes pregnant, while participating in the trial, will discontinue trial intervention.

8.5.1.3 *Lactation*

Not applicable.

8.5.2 **Participants Whose Partners Become Pregnant**

Details about all pregnancies in participants' partners will be collected from the participant's signing of the ICF and until 60 days after the last dose of trial intervention. Collection of pregnancy data from a participant's partner requires the partner's informed consent.

To the extent possible, the investigator will collect follow-up information on the outcome of the pregnancy and the neonate, and the information will be forwarded to the sponsor.

Once a partner pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours.

8.6 **Medical Device Product Complaints for Drug/Device Combination Products**

Not applicable.

8.7 **Pharmacokinetics**

For participants in the elritercept treatment arm only, blood samples will be collected for measurement of serum concentrations of elritercept as specified in the SoA (Section 1.3). A second set of PK samples is required if a participant's dose is up-titrated to 5.0 mg/kg. These PK samples should be collected predose on D1, D8, D15 of the dose up-titration cycle and D1 of the subsequent cycle.

The actual date and time (24-hour clock time) of each sample will be recorded. Instructions for the collection and handling of biological samples will be provided separately.

Any remaining serum from PK samples may be used for exploratory analyses of additional biomarker readouts, for example, cytokines.

Sample retention is described in Appendix 14.1. Samples collected for analyses of elritercept concentration may also be used to characterize safety or efficacy variables related to concerns arising during or after the trial. Further details are provided in Appendix 14.2.

8.8 **Genetics**

Genotyping will not be performed in this trial. Somatic mutation analysis for MDS disease will be performed as described in Section 8.9.3.

8.9 Biomarkers

Biomarkers from blood and bone marrow samples will be analyzed and evaluated to further understand elritercept MoA and its downstream biological effects, including potential effects beyond increased red blood cell production which may also lead to additional benefits/improved QoL. In addition, analysis of baseline biomarkers (for example, SF3B1 mutations) and potential association with biological and clinical responses will also be evaluated. These analyses may provide further insight into how elritercept may differ from EPO in the type and amplitude of downstream responses.

Since transfusions may impact these biomarkers, it is essential that these samples are collected before the transfusion if there is one on the same day.

Refer to the SoA (see Section 1.3) and Laboratory Manual for more details.

8.9.1 Circulating Clinical Biomarkers

Serum will be collected (see Section 1.3) to further understand the effects of elritercept on erythropoiesis and additional biological pathways. Specific clinical parameters (see Table 8.e) associated with iron homeostasis (for example, ferritin, hepcidin), bone metabolism (for example, bone specific alkaline phosphatase), and cardiac function (for example, NT-proBNP) may be assessed. Any remaining serum may be used for additional exploratory analyses, such as follow-up studies from these results.

Table 8.e Clinical Biomarker Assessments

- | |
|--|
| <ul style="list-style-type: none">• EPO• TPO• Serum iron• NTBI• Ferritin• Transferrin• Transferrin saturation• Total iron binding capacity• Soluble transferrin receptor level• Hepcidin• NT-proBNP• Bone-specific alkaline phosphatase |
|--|

8.9.2 Exploratory Circulating Biomarkers

Serum samples will also be collected (see Section 1.3) for analyses of exploratory circulating biomarkers, which may include but are not limited to TGFb family members, inflammatory cytokines, and additional bone metabolism biomarkers.

CONFIDENTIAL

Whole blood will also be collected (see Section 1.3) for exploratory analyses of RNA to understand downstream biological effects of elritercept and how they differentiate from EPO treatment, especially during early cycles when blood transfusions are less likely to be confounding.

Further information on sample retention and future use of samples will be described in Appendix 14.0.

8.9.3 Exploratory Mutational Analyses

As part of disease assessment, bone marrow samples will be used to sequence select genes which are commonly mutated in MDS, such as SF3B1, TP53, TET2, ASXL1. These mutations will also be used to determine IPSS-M risk scoring. Exploratory analyses will be conducted to evaluate associations of baseline mutations with efficacy and changes in variant allele frequency with treatment. In addition, correlation with baseline IPSS-M risk scores and changes in IPSS-M with treatment can also be evaluated.

Any remaining bone marrow samples from screening and on-trial assessments may be used for additional exploratory studies, such as RNA analyses, additional protein staining, and so on.

Since bone marrow aspirate can be limited and is used for other analyses (for example, cytogenetics, pathology), it is possible that there will not be sufficient material for sequencing. A peripheral blood sample will be collected at baseline for additional mutation analyses as needed. Note these mutations are expected to be somatic mutations (that is, not inheritable) that occur as MDS progresses.

Sample retention and further use of samples will be described in an appendix in the Appendix 14.0.

8.10 Immunogenicity Assessments

For participants in the elritercept treatment arm only, antibodies to elritercept will be evaluated in serum samples collected according to the SoA (Section 1.3). See the Laboratory Manual for details. Samples should be collected before elritercept is administered on a dosing day, and optionally at unscheduled visits for a participant who experiences an AE considered by the investigator to be consistent with hypersensitivity/infusion-related reaction. A sample will be assessed for neutralizing ADA if a positive ADA is detected. Additionally, serum samples should also be collected at the final visit from participants who discontinued trial intervention or were withdrawn from the trial. These samples will be tested by the sponsor or sponsor's designee.

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

The detection and characterization of antibodies to elritercept will be performed using a validated assay. Samples collected for detection of antibodies to elritercept will also be evaluated for elritercept serum concentration to enable interpretation of the antibody data.

Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of elritercept.

Any remaining serum from immunogenicity/ADA samples may be used for exploratory analyses of additional biomarker readouts, for example, cytokines.

Sample retention and further use of samples is described in Appendix [14.0](#).

8.11 Medical Resource Utilization and Health Economics

To characterize healthcare resource utilization among participants treated with elritercept as compared with participants receiving epoetin alfa, healthcare resource utilization data will be collected as indicated in the SoA (Section [1.3](#)), at the first day of each cycle starting on Cycle 2 (C2D1) and at EOTx using the eCRF. For participants who have a hospitalization, the site-designated staff will be asked to provide information on the reason for hospitalization (for example, disease progression, MDS-related illness (for example, RBC or platelet transfusions for anemia or thrombocytopenia, respectively; infections, and so on), treatment-related AE), use of ambulance, hospital admissions originating in the emergency department, and days of hospitalization by treatment setting (regular hospital ward versus intensive care unit). Other types of healthcare resource utilization collected through routine trial activities will include the number of unplanned trial-site visits, diagnostic procedures, treatment interventions not requiring hospitalization, such as those required for treatment-related AEs and MDS-related illness, and the use and daily dose of iron chelation therapy for iron overload.

9.0 STATISTICAL CONSIDERATIONS

A SAP will be prepared and finalized before the first participant's written informed consent is obtained. The SAP will provide further details regarding the definition of analysis variables and the statistical analysis methodology to address all trial objectives.

9.1 Analysis Sets

ITT analysis set: All randomized participants. Participants will be analyzed according to the treatment they are randomized to receive, regardless of any errors of dosing. The ITT Population will be used for all analyses of efficacy and baseline characteristics.

Per-protocol analysis set: The subset of ITT analysis set without major protocol deviations determined to potentially affect the ability to interpret efficacy or safety, or violate ethical participation in the trial. The per protocol analysis set will be used for sensitivity analyses of the efficacy primary endpoint and additional endpoints as applicable.

Safety analysis set: Participants who received at least 1 dose or partial dose of trial intervention. Participants will be analyzed according to the actual treatment received, elritercept or epoetin alfa. The Safety Population will be used for all safety analyses.

Pharmacokinetic analysis set: Participants from the subset of the Safety analysis set who receive at least 1 dose of elritercept and have at least 1 measurable (above the lower limit of quantitation) concentration of elritercept in plasma.

Immunogenicity analysis set: Participants from the subset of the Safety analysis set who receive ≥ 1 dose of elritercept and have baseline and ≥ 1 posttreatment immunogenicity assessment.

Clinical outcome assessment analysis set: Participants from the subset of the ITT population who have an HRQoL assessment at baseline and at least 1 postbaseline assessment.

9.2 Analyses Supporting Primary Objective(s)

9.2.1 Statistical Model, Hypothesis, and Method of Analysis

9.2.1.1 Primary Endpoint

The primary efficacy endpoint responders are defined as participants who receive at least a dose of trial intervention and achieved RBC-TI for a minimum of 12 consecutive weeks with concurrent increase from baseline in mean Hgb 1.5 g/dL through the first 24 weeks on-trial.

For the primary endpoint, the response rate will be calculated using the number of responders divided by the number of participants in each treatment arm in the ITT population.

The null hypothesis is that the response rates are the same between the elritercept arm and the epoetin alfa arm. The alternative hypothesis is that the response rate in the elritercept arm is not the same as the response rate in the epoetin alfa group.

The CMH test will be used to test the difference between the response rates of two treatment arm in the ITT population with the randomization stratification factors as strata, at the 2-sided alpha of 0.05. The Cui-Hung-Wang procedure will be applied at the primary analysis to control the type I error due to sample size re-estimation.

Adjustment may be made to the CMH test when one or more strata have too few participants (such as dropping a stratification factor from the CMH test). The rule for the adjustment will be pre-specified in the SAP.

Details on assessment definitions will be included in Appendix [16.0](#).

9.2.2 Handling of Intercurrent Events of Primary Estimand(s)

Two major intercurrent current events are identified in the trial:

- Treatment discontinuation prior to response.
- Protocol-prohibited medication usage (concomitantly or as subsequent treatment) prior to response.

A hybrid approach will be used to handling the intercurrent events: the intercurrent treatment discontinuation prior to response will be handled using the treatment policy strategy whereas protocol-prohibited medication usage will be handled using the composite strategy.

Under this hybrid approach, a participant who did not achieve response prior to start of a protocol-prohibited medication will be considered as a non-responder. Whereas a participant who achieved response before start of a protocol-prohibited medication, regardless of whether it was before or after treatment discontinuation, will be considered as a responder.

This hybrid approach ensures the efficacy of the trial intervention is isolated from the confounding effects introduced by the protocol-prohibited medications.

9.2.3 Handling of Missing Data

For efficacy endpoints based on transfusion independence, including the primary and all key secondary endpoints, a participant with missing transfusion or Hgb data due to intercurrent events will be considered as a nonresponder if response has not been achieved before the intercurrent events.

For an efficacy endpoint that requires a mean Hgb change from baseline over a minimum period of time (8, 12, or 16 weeks), if the baseline Hgb data is missing, the participant will be considered as a nonresponder. If there is insufficient postbaseline Hgb data during the period of time to accurately estimate the mean Hgb change from baseline, the participant will also be considered as a nonresponder.

For the additional alpha-controlled secondary endpoint of favorable fatigue response with no RBC transfusion between the end of Week 12 and the end of Week 24, missing FACIT-Fatigue scale scores will be addressed through imputation.

Further details of missing data handling and imputation strategy will be described in the SAP.

9.2.4 Sensitivity Analysis

Per-protocol analysis set might be used for the efficacy analyses. Additional sensitivity analysis may be specified in the SAP.

9.2.5 Supplementary Analysis

The treatment policy strategy might be used to handle intercurrent event, that is, the occurrence of the intercurrent event is irrelevant, that is, the value of the endpoint is used regardless of whether the intercurrent event occurs or not.

9.2.6 Subgroup Analyses

Subgroup analyses will be performed for the primary and key secondary endpoints relative to the baseline randomization stratification factors such as RS status, sEPO level, transfusion burden according to IWG 2006 transfusion burden categories and nonstratification variable (SF3B1

mutations). Additional subgroup analyses will be conducted for the primary endpoint, key secondary, and other endpoints, as appropriate.

9.3 Analysis Supporting Secondary Objectives

For each key secondary endpoint, the response rate will be calculated using the number of responders divided by the number of participants in each treatment arm in the ITT population.

The null hypothesis for each key secondary endpoint is that the response rates are the same between the elritercept arm and the epoetin alfa arm. The alternative hypothesis is that the response rate in the elritercept arm is not the same as the response rate in the epoetin alfa arm.

A fixed-sequence approach will be used to control the overall type I error rate for testing of the primary endpoints, all key secondary endpoints and 1 additional secondary endpoint. The key secondary endpoints along with the additional alpha-controlled secondary endpoint, listed in [Table 3.c](#), will only be tested after the primary endpoint reached statistical significance and with the following testing order:

1. RBC-TI for a minimum 16-week period from C1D1 through Week 24.
2. RBC-TI for a minimum 12-week period from C1D1 through Week 24.
3. RBC-TI for a consecutive 24-week period from C1D1.
4. Favorable fatigue response based on FACIT-Fatigue scale scores with no RBC transfusion between the end of Week 12 and the end of Week 24.

All the above endpoints will be tested at a 2-sided alpha level of 0.05.

The CMH test will be used to test the difference between the response rates of two treatment arms in the ITT population with the randomization stratification factors as strata.

For the key secondary endpoints, intercurrent events handling will follow the same approach as the primary endpoint.

For the secondary PRO endpoints, a Psychometric Analysis Plan will be prespecified and executed on blinded data from the trial prior to the primary analysis in order to generate score cutoffs required for endpoint evaluation. A threshold score for the FACIT-Fatigue will be used to distinguish groups of participants who have low or high fatigue at baseline. Score thresholds for meaningful changes in PROs (EORTC QLQ-C30 physical function and fatigue scales, FACT-An Anemia scale, and FACIT-Fatigue scale) will be used to define endpoints based on clinically meaningful improvement or deterioration.

For the additional alpha-controlled secondary endpoint of favorable fatigue response with absence of RBC transfusion between the end of Week 12 and the end of Week 24, response will be defined separately for the low and high baseline fatigue subgroups. For the high fatigue subgroup, a participant will be classified as a responder if having a meaningful improvement in FACIT-Fatigue score at two or more consecutive assessments with no RBC transfusion between the end of Week 12 and the end of Week 24 and as a nonresponder otherwise. For the low

fatigue subgroup, a participant will be classified as a responder if having FACIT-Fatigue scores maintained above the baseline threshold used in fatigue level classification, no meaningful deterioration in FACIT-Fatigue score, and no RBC transfusion between the end of Week 12 and the end of Week 24 and as a nonresponder otherwise. The CMH test will be used to test the difference between the response rates of two treatment arms in the ITT population with the randomization stratification factors as strata.

Other secondary endpoints are analyzed without controlling type I error rate.

Similar to the primary endpoint, adjustment may be made to the CMH test for secondary endpoints when one or more strata have too few participants (such as dropping a stratification factor from the CMH test). The rule for the adjustment will be prespecified in the SAP.

Time to progression to AML: participants with diagnosis of AML will be considered to have had an event. Participants who have not progressed to AML at the time of analysis will be censored at the last assessment date, which does not indicate progression to AML.

9.3.1 Other Secondary and Exploratory HRQoL Endpoints

The completion rate and available data rate will be calculated for each PRO at each assessment point. The proportion (n) of participants with or without meaningful improvement in EORTC QLQ-C30 (physical function, dyspnea, and fatigue), FACT-An Anemia, and FACIT-Fatigue scale scores at the end of Week 24 and the end of Week 48 will be reported. Time to confirmed improvement and time to confirmed deterioration in EORTC QLQ-C30 (physical function, dyspnea, and fatigue), FACT-An Anemia, and FACIT-Fatigue scale scores through the end of Week 24 and through the end of Week 48 will be summarized and plotted using Kaplan-Meier curves. Events will be defined as meaningful improvement (or worsening) in PRO score at two or more consecutive assessments. Median values along with two-sided 95% CIs will be calculated. Changes from baseline in EORTC QLQ-C30 (physical function, dyspnea, and fatigue), FACT-An Anemia, and FACIT-Fatigue scale scores will be analyzed using mixed models for repeated measures controlling for treatment and stratification factors as fixed effects and the baseline PRO score as a covariate. Summary statistics for all PRO scores (mean score or score change, SD, range, 95% CI, n) will be reported by treatment arm at each assessment point.

Exploratory analyses will include the application of TWiTR procedure to evaluate patient benefit by integrating transfusion status with clinical outcomes and PROs ([Mesa et al. 2025](#); [Zeidner et al. 2023](#)). TWiTR partitions each participant's on-trial time into intervals defined by clinically relevant states (that is, transfusion dependence, relapse, and TWiTR. These time intervals can be weighted using health state utilities to obtain Q-TWiTR estimates that reflect the duration and HRQoL of each state. The average (95% CI) proportion of time spent in each state through Week 24 and Week 48, with and without quality adjustment, will be compared between treatment arms. Shorter duration of TD and longer duration of TWiTR suggest improved survival quality.

All analyses will be performed without control for Type I error rate. Further details regarding analysis procedures will be provided in the SAP.

9.3.2 PK Analyses

Serum elritercept concentration data will be summarized using descriptive statistics at each scheduled time point, as appropriate. The elritercept concentration-time data will be used in an integrated population-PK and subsequent exposure-response analyses. These analyses will be reported separately.

9.3.3 Immunogenicity Analyses

ADA data will be analyzed based on immunogenicity-evaluable analysis set. The percentage of participants who have no detectable ADA at baseline and become positive in this assay, the percentage of participants who have no detectable ADA at baseline and remain negative without detectable ADA, and those who have detectable and are positive for ADAs at baseline that increase or decrease in titer over the course of treatment will be summarized. Where applicable, NAb titers will also be assessed. Summaries will be provided separately for each trial phase and by dose, as applicable. All analyses will be descriptive and exploratory in nature.

9.4 Analysis of Exploratory Objective(s)

9.4.1 Clinical and Translational Biomarkers

Summaries will be provided for laboratory values from blood and bone marrow samples including but not limited to neutrophils, platelets, serum ferritin, and mutations. Additional exploratory biomarkers may be reported separately.

All analyses will be descriptive and exploratory in nature.

9.4.2 Healthcare Resource Utilization

Healthcare resource utilization data will be collected and summarized by treatment arms. Healthcare resource utilization includes an aggregation of hospitalizations, concomitant iron chelation therapy, and surgeries, as well as RBC transfusion utilization.

9.5 Safety Analyses

Safety data, including AEs, laboratory data, vital signs, weight, echocardiograms and ECGs will be summarized for the Safety Population by treatment arm.

A TEAE is defined as an AE that commences on or after the first dose of the trial intervention and within 60 days after the last dose of the trial intervention, or analysis cutoff date, whichever is earlier. AEs will be coded using MedDRA. TEAEs will be summarized by MedDRA SOC and PT. The number and percentage of participants with TEAEs, treatment-emergent SAEs, treatment-related TEAEs, treatment-related treatment-emergent SAEs, and TEAEs leading to treatment discontinuation will be summarized by treatment arm.

Hematologic and non-hematologic laboratory abnormalities will be listed and summarized according to the NCI-CTCAE version 5 or higher by treatment arm.

Laboratory data and vital signs will be summarized at each scheduled time point. Descriptive statistics for both observed values and changes from baseline will be presented by treatment arm.

Exposure-adjusted rates of TEAEs may be presented by treatment arm.

9.6 Other Analyses

Not applicable.

9.7 Interim Analyses

One IA is planned after approximately 110 participants have completed 24 weeks of assessments from C1D1 or initiated therapy with a prohibited medication before reaching 24 weeks. This IA is for futility analysis and sample size re-estimation. No statistical significance claim will be made for any endpoint at the IA, therefore no alpha will be allocated.

Conditional power of the primary endpoint for a minimal sample size of 210 will be calculated at this IA. The trial will stop for futility if the conditional power is smaller than 0.1. If the futility is not claimed, the trial will continue to the primary analysis. On the basis of the result at IA, the planned sample size may be increased up to 300, if the observed treatment effect is promising but not large enough to yield the likely conclusion of statistical significance at the primary analysis using the originally planned minimal sample size. It is also possible for the sample size to remain unchanged as the result of the IA. The Cui-Hung-Wang testing procedure will be applied to the primary analysis to control the type I error rate.

The IA will be conducted by the independent statistical center and presented for review to the DMC. During the closed session of the DMC meeting, the DMC will compare the conditional power for the primary endpoint based on the IA result with the prespecified sample size adaptation rules and recommend to the sponsor the futility or adaptation decision. This recommendation will be documented by the DMC. The results of the IA will remain blinded to the sponsor until primary analysis of the trial.

9.8 Primary, Secondary and Final Analyses

The primary analysis of the trial is planned after all enrolled participants have completed 24 weeks of assessment or discontinued before reaching 24 weeks. This will be the final analysis for all the endpoints that require 24 weeks of assessment, including all the primary and key secondary endpoints. Other endpoints that require a longer period of assessment may also be reported at this analysis.

The secondary analysis of the trial is planned after all enrolled participants have completed 48 weeks of assessment or discontinued before reaching 48 weeks. This will be the final analysis for all the endpoints that require 48 weeks of assessment. Other endpoints that require a longer period of assessment may also be reported at this analysis.

The final analysis of disease progression and overall survival is planned 5 years after randomization of the last participant.

9.9 Sample Size Determination

The total sample size is based on the adaptive sample size re-assessment approach. For the purpose of sample size calculation, the primary endpoint response rate is assumed to be 63% for the elritercept arm and 40% for the epoetin alfa arm in the optimal scenario. A minimum total of 210 participants will provide 90% power (after accounting for the futility analysis) to detect this 23% difference in response rate, with a minimal detectable effect size of 13.5%.

In the maximum sample size scenario, the primary endpoint response rate is assumed to be 60% for the elritercept arm and 40% for the epoetin alfa arm. A maximum of 300 participants will provide 90% power (after accounting for the futility analysis) to detect this 20% difference in response rate, with a minimal detectable effect size of 11.3%.

The power calculation is based on the test statistic of the difference of proportions using pooled estimate of variance with a 2-sided alpha level of 0.05.

Conditional power of the primary endpoint for a minimal sample size of 210 will be calculated at IA. If futility is not claimed, the conditional power will be calculated. If the conditional power falls in the favorable zone or unfavorable zone, the PA with approximately 210 participants will remain unchanged. If the conditional power falls in the promising zone, the number of participants will be determined according to a prespecified sample size adaptation rule, with a cap of approximately 300 participants. No efficacy claim will be made in this IA.

Enrollment of RS+ and RS- participants will be targeted to the range of 60% ~ 70% and 30% ~ 40%, respectively.

9.10 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial participants. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria or trial procedures.

The site should document all protocol deviations in the participant's source documents. In the event of a significant deviation, the site should notify the sponsor. Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the participant, or confound interpretation of the trial efficacy and safety assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated, it may be reported to regulatory authorities and IRB/ECs as a serious breach of GCP and the protocol.

Protocol deviations will be identified prior to database lock and significant ones will be listed in the clinical study report.

CONFIDENTIAL

10.0 GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT

10.1 Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines.
- ICH GCP Guidelines.
- Applicable laws and regulations (for example, EU CTR).

10.1.1 Investigator Responsibilities

10.1.1.1 Introduction

Each investigator will conduct the trial according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the [List of Investigator Responsibilities](#) in Section 10.1.1.2.

The trial is being funded by Takeda. Payments for the conduct of the trial that will be made to trial sites (and, if applicable, investigators and/or other trial staff) will be specified in the Clinical Trial Site Agreement(s). All investigators and subinvestigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and subinvestigator before the trial starts at their trial site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor before the start of the trial at their site.

All institutional affiliations of the investigator and subinvestigator should be declared on their curriculum vitae, which must be provided to sponsor before the start of the trial.

10.1.1.2 List of Investigator Responsibilities

Clinical research trials sponsored by the sponsor are subject to ICH GCP and all applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the Statement of Investigator (Form FDA 1572), which must be completed and signed before the investigator may participate in this trial.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the trial in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should

implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

4. Ensure that trial-related procedures, including trial-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential participants before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
6. Secure prior approval of the trial and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to participants. Make at least yearly reports on the progress of the trial to the IRB/IEC, and issue a final report within 3 months of trial completion.
8. Ensure that requirements for informed (e)consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed (e)consent from each trial participant, and document the date of (e)consent in the participant's medical chart. Valid informed (e)consent is the most current version approved by the IRB/IEC. Each ICF should contain a participant authorization section that describes the uses and disclosures of a participant's personal information (including personal health information) that will take place in connection with the trial. If an ICF does not include such a participant authorization, then the investigator must obtain a separate participant authorization form from each participant or the participant's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, and so on, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied trial interventions, and return all unused sponsor-supplied trial interventions to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

10.1.1.3 Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (that is, the UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the investigator for the trial and/or other clinical trials.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other trial interventions used in other clinical trials that may contain the same chemical compound present in the trial intervention.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting investigator site contact information, trial details, and results on publicly accessible clinical trial registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

The investigator acknowledges and consents to the use of this personal information by Takeda and other parties for the purposes described above.

10.1.1.4 Investigator Agreement

Please refer to the following page for the Investigator Agreement.

CONFIDENTIAL

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this trial in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and wellbeing of trial participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 8.4 of this protocol.
- Terms outlined in the clinical trial site agreement.
- Responsibilities of the investigator (Section 10.1.1.2).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Section 10.1.1.3 of this protocol.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

CONFIDENTIAL

10.1.2 Sponsor Responsibilities

The trial sponsor and any third party to whom aspects of the trial management or monitoring have been delegated will undertake their assigned roles for this trial in compliance with all applicable industry regulations, current ICH GCP Guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the trial sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect trial data, participants' source documents, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the trial. The sponsor (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required before release of trial intervention for shipment to the site.

10.1.2.1 *Serious Breach of Protocol or EU Clinical Trial Regulation*

Takeda will notify the concerned EU Member States of a serious breach of EU CTR or the applicable protocol version through the EU portal not later than 7 days after becoming aware of the breach. In this instance a "serious breach" is one likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of trial data. All parties involved in the conduct of the clinical trial must immediately report any events they encounter that might meet the definition of a serious breach to the contact point designated in the site manual.

10.2 Committees

10.2.1 Steering Committee

The steering committee will be formed and comprise of approximately 10 hematology-oncology medical experts in MDS who may or may not be involved in the trial. The steering committee will provide guidance regarding the standard of care for this participant population and expert advice regarding the design of the trial and proposed analyses. The steering committee will receive periodic updates on the trial progress and may provide recommended clinical guidance to support conduct of the trial and provide input regarding the interpretation of results. The Steering Committee Charter will define the responsibilities and expectations of the committee. The Trial Clinician will be responsible for the organizational oversight of the committee.

10.2.2 DMC

According to ICH E6 an external DMC or an internal review committee (for example, Independent Data Monitoring Committee, Data and Safety Monitoring Committee, Monitoring Committee, Data Monitoring Committee) may be established by the sponsor to assess at intervals

the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

The minimal description of the IDMC should include:

- Composition (number of members and expertise).
- Frequency of meetings/assessments.
- Purpose and authority.
- Scope of data review.

Details of the IDMC or internal review committee will be captured in a charter before the start of the trial.

An external, independent DMC will be formed and the voting members will comprise of a minimum of 3 hematology-oncology medical experts not involved in this trial including one assigned as Chairperson, and an independent statistician not involved in this trial. Additional ad hoc members may be invited to provide expert advice, as appropriate.

The DMC Charter will specify the roles and responsibilities of the DMC members as well as that of the sponsor's DMC Lead, DMC Coordinator and Statistical Coordinating Center. The Charter will specify the organizational meeting and expectations for subsequent data review meetings including cumulative safety data review and efficacy data assessment in accordance with this protocol. The Charter will specify the requirements for the data review meetings including role of the sponsor. After each data review meeting the DMC will provide a recommendation to sponsor to continue the trial with or without modification or to terminate the trial.

10.3 Informed Consent Process

Written and electronic consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the participant's personal and personal health information for purposes of conducting the trial, including the use of electronic devices and associated technologies (if applicable). The ICF and the participant information sheet (if applicable) further explain the nature of the trial, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the participant's freedom to withdraw at any time without giving a reason and without prejudice to further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the participant authorization form. The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) must be written in a language fully comprehensible to the prospective participant. It is the responsibility of the investigator to explain the detailed elements of the ICF, participant authorization form (if applicable), and participant information sheet (if applicable) to the participant. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the participant is not capable of rendering adequate written or electronic informed consent, then the participant's legally acceptable representative may provide such consent for the participant in accordance with applicable laws and regulations.

The participant, or the participant's legally acceptable representative, must be given ample opportunity to (1) inquire about details of the trial and (2) decide whether to participate in the trial. If the participant, or the participant's legally acceptable representative, determines that the participant will take part in the trial, then the ICF and participant authorization form (if applicable) must be (e)signed and dated by the participant, or the participant's legally acceptable representative, at the time of (e)consent and before the participant enters into the trial. Participants or their legally acceptable representatives should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink in the case of written informed consent. The investigator must also (e)sign and date the ICF and participant authorization (if applicable) at the time of (e)consent and before the participant enters into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once (e)signed, the original ICF, participant authorization form (if applicable), and participant information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the participant signs the informed consent in the participant's medical record. Copies of the signed ICF, the signed participant authorization form (if applicable), and participant information sheet (if applicable) shall be provided to the participant.

All revised ICFs must be reviewed and signed by relevant participants or the relevant participant's legally acceptable representative in the same manner as the original informed (e)consent. The date the revised (e)consent was obtained should be recorded in the participant's medical record, and the participant should receive a copy of the revised ICF.

10.3.1 Informed Consent for Rescreening

A screening participant who is determined to not meet eligibility requirements after completing screening may be rescreened for the trial at a later date. The screening participant will need to re-consent at the time when the repeated trial procedures for screening are initiated.

10.3.2 Informed Consent for Use of Remaining Samples for Future Research

Participants will be asked to consent to future research using remaining samples, specifically, leftover bone marrow tissue, blood, and serum/plasma samples collected as part of the trial. Retained samples may be analyzed using new assays or platforms to test hypotheses relevant to disease biology outside of the elritercept clinical trial. Research analyses may include, but are not

CONFIDENTIAL

limited to, measurement of serum/plasma biomarkers, targeted DNA and RNA sequencing, and immunohistochemistry.

If a participant consents, leftover samples may be retained and stored for other possible additional future analysis and assay development if allowed by country specific guidelines and regulations. Any retained samples will be de-identified and will not be labeled with participant identifying information. Leftover samples will be destroyed either after 15 years from the end of the trial or per local regulations, whichever is stricter.

10.4 Data Protection

10.4.1 Participant Confidentiality

The sponsor and designees affirm and uphold the principle of the participant's right to protection against invasion of privacy. Throughout this trial, a participant's source data will be linked to the sponsor's clinical trial database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited participant attributes, such as sex, age, or date of birth, and participant initials may be used to verify the participant and accuracy of the participant's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (that is, US FDA, UK MHRA, Japan PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the participant's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a participant's trial participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization of the participant as part of the informed (e)consent process (see Section 10.3).

Copies of any participant source documents that are provided to the sponsor must have certain identifying personal information removed, for example, participant name, address, and other identifier fields not collected on the participant's eCRF.

10.4.2 Responsibilities Following Termination or Suspension

If the trial is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/IECs are notified as appropriate. The sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements.

Additionally, the discontinuation of a registered clinical trial that has been posted to a designated public website will be updated accordingly.

If the trial is prematurely terminated or suspended, The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

CONFIDENTIAL

The sponsor will make an end-of-trial declaration to the relevant competent authority as required by Article 10(e) of Directive 2001/20/EC and the EU CTR.

10.4.3 Serious Data Breach Prevention and Reporting

If a serious data breach affecting personal data is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventive actions in response. These actions will be documented, and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of trial participants, this would be done through the investigator.

Takeda applies certain measures to protect participants' personal data and prevent data breaches, detailed in a separate Compliance with National Requirements on Data Protection document.

10.5 Early Site Closure or Trial Termination

10.5.1 Decision Rights for Site Closure and Trial Termination

The sponsor may suspend or terminate the trial, or part of the trial, at any time for any reason. The sponsor reserves the right to close the trial site at its sole discretion. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents have been collected and a trial-site closure visit has been performed.

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

10.5.2 Criteria for Early Trial Site Closure

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

- For trial termination:

Discontinuation of further trial intervention development

- For site termination:

Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

Total number of participants included earlier than expected

11.0 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1 Quality Tolerance Limits

QTLs will be predefined in the Centralized Monitoring Plan to identify systematic issues that can impact participant safety and/or reliability of trial results. These predefined parameters will be monitored during the trial, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

11.2 Data Quality Assurance

11.2.1 Sponsor or Designee Responsibilities for Data Quality Assurance

The sponsor or designee is responsible for the data management of this trial, including quality checking of the data.

Monitoring details describing strategy, including definition of trial critical data items and processes (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in functional plans and systems as referenced in the Integrated Quality Risk Management Plan.

The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).

11.2.2 Investigator Responsibilities for Data Quality Assurance

All participant data relating to the trial will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Guidelines.

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. Additionally, investigators must promptly notify Takeda of any trial-related regulatory agency inspections and will be expected to provide Takeda with a copy of the inspection report.

Essential records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator as described in [Section 15.1](#)

11.3 Source Data

11.3.1 Introduction

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. All key data must be recorded in the participant's source documents unless otherwise noted in the protocol. It is expected that information transcribed in the eCRF can be traced to source documents.

11.3.2 Investigator Expectations for Source Data

The investigator as listed on the US FDA Form 1572 is responsible for maintaining source documents. The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (for example, via audit trail).

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous source documents or transfer records, depending on the trial.

Source documents are filed at the investigator's site. The investigator must provide direct access to inspect facilities, including original source records relevant to this trial (regardless of media), to the sponsor's authorized representatives; respective national, local, or foreign regulatory authorities; the IRB/IEC; and auditors. Current records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (for example, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor. The eConsent form includes a statement granting this access to source data.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

11.3.3 Trial Monitor Expectations for Source Data

Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

11.3.4 Definition of Source Data

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Electronic

source data are data initially recorded in electronic form. Examples of source data include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aids or evaluation checklists, pharmacy dispensing records, audio recordings of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

12.0 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY

12.1 Further Details and Clarifications on the AE Definition

Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under trial, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Abnormal laboratory and other abnormal investigational findings (for example, physical examination, ECG) should not be reported as AEs unless they lead to treatment modification or discontinuation, require therapeutic intervention, or are otherwise considered to be clinically significant by the investigator.

12.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a participant who has signed informed consent to participate in a trial but before administration of any trial intervention; it does not necessarily have to have a causal relationship with trial intervention.

12.2 Further Details and Clarifications on the SAE Definition

Expected progression, signs or symptoms of anemia, unless more severe than expected, do not meet the SAE criteria.

12.3 Severity

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0 or higher. The criteria are provided in the site manual.

12.4 Causality

Relationship of the event to trial intervention administration (that is, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the trial intervention?

13.0 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

13.1 Contraception and Pregnancy Testing

13.1.1 Definitions Related to Childbearing Potential

13.1.1.1 *Participants of Childbearing Potential*

For the purpose of this trial, a person of female birth sex is considered a POCBP, that is, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or hormonal replacement therapy.

However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

13.1.1.2 *Participants of Male Birth Sex who are Fertile*

For the purpose of this trial, a person of male birth sex is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

13.1.2 Contraception

13.1.2.1 *Highly Effective, Acceptable, and Unacceptable Contraception Methods*

13.1.2.1.1 *Highly Effective Contraception Methods*

Birth control methods may be considered highly effective if they can achieve a failure rate of less than 1% per year when used consistently and correctly, including:

- Combined (estrogen- and progestogen-containing hormonal contraception associated with inhibition of ovulation:

Oral.

Intravaginal.

Transdermal.

- Progestogen-only hormonal contraception associated with inhibition of ovulation

Oral.

Injectable.

Implantable.

- Intrauterine device.
- Intrauterine hormone-releasing system.

CONFIDENTIAL

- Bilateral tubal occlusion.
- Vasectomized partner (highly effective provided that partner is the sole sexual partner of the POCBP trial participant and the vasectomized partner has received medical assessment of the surgical success).
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of the risk associated with the trial intervention[s]. Reliability of abstinence should be evaluated in relation to trial duration and the preferred and usual lifestyle of the trial participant.).

13.1.2.1.2 *Acceptable Contraception Methods*

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.

Note that a combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, contraception methods.

13.1.2.1.3 *Unacceptable Contraception Methods*

The following birth control methods are considered unacceptable for use in clinical trials:

- Periodic abstinence.

Calendar.

Symptothermal.

Postovulation.

- Withdrawal (coitus interruptus).
- Spermicides only.
- Lactational amenorrhea method.

Note also that female and male condoms should not be used together.

13.1.2.2 *Duration of Contraception Use*

13.1.2.2.1 *Contraception Duration for POCBP*

POCBP must practice highly effective methods of contraception from the time of signing of the ICF through 60 days after the last dose of trial intervention.

CONFIDENTIAL

13.1.2.2.2 Contraception Duration for Fertile Men

Fertile men must practice effective methods of contraception during the entire trial intervention period and through 60 days after the last dose of trial intervention.

13.2 Clinical Laboratory Tests

Not applicable.

13.3 Publication and Clinical Trial Registration and Disclosure Policies

During and after the trial, only the sponsor may make trial information available to other trial investigators or to regulatory agencies, except as required by law or regulation.

13.3.1 Publication Policy

The sponsor may publish any data and information from the trial (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication venue (for example, congress, journal) will appropriately reflect contributions to the production, review, and approval of the document.

13.3.2 Clinical Trial Registration and Disclosure

Per Takeda's policy/standards and applicable laws, regulations, and guidance, Takeda discloses information on clinical trials, including results, on ClinicalTrials.gov and other applicable public registries and websites, including the Takeda corporate site.

13.4 Country/Region-Specific Differences

Not applicable.

13.5 Prior Protocol Amendments

Not applicable.

14.0 APPENDIX: SAMPLE RETENTION AND USE

14.1 Sample Retention

Bone marrow tissue, blood and serum/plasma samples collected as part of the trial will be stored and may be used for research purposes up to 15 years after the date of trial completion. Samples will be destroyed by a third-party vendor per company standard operating procedures. Samples will be stored according to the laboratory manual. If a participant withdraws consent, the investigator must inform the sponsor immediately and the samples will be discarded following the local procedure (that is, where the sample resides at the time of withdrawal). The tests performed with these samples are not intended to make determinations about a participant's health or the likelihood that a participant will develop any disease, so no test results will be

provided to the investigator or put into a participant's medical record. Test results should not be discussed with a participant unless required by local law.

14.2 Sample Use for Future Research Purposes

Bone marrow tissue, blood and serum/plasma samples collected as part of the trial under sample retention (Section 8.2.3, MDS Disease Assessment; Section 8.7, [Pharmacokinetics](#); Section 8.8, [Genetics](#); Section 8.9, [Biomarkers](#); and Section 8.10 Immunogenicity) may be analyzed using new assays or platforms to test hypotheses relevant to mechanism of action and disease biology separate from this clinical trial. Research analyses may include, but are not limited to, measurement of serum/plasma biomarkers, targeted DNA and RNA sequencing, and immunohistochemistry.

15.0 APPENDIX: RECORD RETENTION

15.1 Record Retention Responsibilities of the Investigator/Site

To enable evaluations or audits from regulatory authorities, the investigator and the head of the trial site must retain the records shown in Section 15.1.1 for the duration shown in 15.1.2.

15.1.1 Records To Retain

The investigator and the head of the trial site agree to keep the records stipulated in this section and supporting documentation, including but is not limited to:

- Trial-specific documents.
- Identification log of all participating participants.
- Source documents.
- Temporary media such as thermal sensitive paper (any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the participant's chart to ensure long-term legibility).
- Source worksheets.
- All original signed and dated informed eConsent forms (including consent to use digital tools and applications, if applicable).
- Participant authorization forms regarding the use of personal health information (if separate from the informed eConsent forms).
- Query responses/electronic copy of eCRFs, including the audit trail.
- Detailed records of drug disposition.

15.1.2 Duration of Record Retention

Records must be retained in accordance with international guidance (ICH) and local or regional requirements. Refer to the trial site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents. No records may be transferred to another location or party without written notification to the sponsor.

The following applies to sites in Japan only.

The investigator and the head of the institution are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the trial intervention is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued).
2. The day 3 years after the date of early termination or completion of the trial.

In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

When proceeding to the local postmarketing trial, the investigator and the head of the institution are required to retain essential relevant documents until the end of re-examination or re-evaluation, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

15.2 Record Retention Responsibilities of the Sponsor

Data collected are stored in the trial master file for the life of the product plus 30 years unless longer retention is required by local laws.

16.0 APPENDIX: METHODOLOGY AND ASSESSMENT CRITERIA

16.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Table 16.a ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (for example, light housework, d office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than

CONFIDENTIAL

Table 16.a ECOG Scale for Performance Status

Grade	Description
	50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source : ([Oken et al. 1982](#)).

16.2 Myelodysplastic Syndromes World Health Organization Classification System (2016)

Table 16.b Peripheral Blood and BM Findings and Cytogenetics of Myelodysplastic Syndromes (MDS)

Name	Dysplastic lineages	Cytopenias ^a	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15% or <5% b	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15% or <5% b	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15% or ≥5% b	BM <5%, PB <1%, No Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15% or ≥5% b	BM <5%, PB <1%, No Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, No Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS with excess blasts (MDSEB)					
MDS-EB-1	0-3	1-3	None or any	BM 5-9% or PB 2-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 5-9% or PB 2-4%, no Auer rods	Any

CONFIDENTIAL

Table 16.b Peripheral Blood and BM Findings and Cytogenetics of Myelodysplastic Syndromes (MDS)

Name	Dysplastic lineages	Cytopenias ^a	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB=1% ^c , no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB=1% ^c , no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15% ^d	BM <5%, PB=1% ^c , no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

^a Cytopenias defined as hemoglobin <10 g/dL, platelet count <100 x 10⁹/L, and absolute neutrophil count <1.8 x 10⁹/L; rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be < 1 x 10⁹/L.

^b If SBDB1 mutation is present.

^c 1% PB blasts must be recorded on at least two separate occasions.

^d Cases with ≥ 15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

Source: (Arber et al. 2016)

CONFIDENTIAL

16.3 INTERNATIONAL PROGNOSTIC SCORING SYSTEM-REVISED (IPSS-R) CLASSIFICATION OF VERY LOW, LOW, OR INTERMEDIATE RISK DISEASE

Table 16.c IPSS-R Prognostic Score Values

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	N/A	Good	N/A	Intermediate	Poor	Very Poor
BM blast, %	≤2	N/A	>2 to <5	N/A	5 to 10	>10	N/A
Hgb (g/dL)	≥10	N/A	8 to <10	<8	N/A	N/A	N/A
Platelets (count/μL)	≥100	50 to <100	<50	N/A	N/A	N/A	N/A
ANC (count/μL)	≥0.8	<0.8	N/A	N/A	N/A	N/A	N/A

Source: ([Greenberg et al. 2012](#))

Table 16.d IPSS-R Cytogenetic Risk Groups

Cytogenetic Prognostic Subgroups	Cytogenetic Abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

Source: ([Greenberg et al. 2012](#); [Schanz et al. 2012](#))

Table 16.e IPSS-R Prognostic Risk Categories/Scores

Risk Category	Risk Score
Very Low	≤1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

Source: ([Greenberg et al. 2012](#)).

16.4 INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR MYELODYSPLASTIC SYNDROMES

Table 16.f Hematologic Improvement According to IWG Criteria (Cheson, 2006)

Hematologic Improvement ^a	Response criteria (responses must last at least 8 week) ^b
Erythroid Response (HI-E) (pretreatment, <11 g/dL)	· Hemoglobin increase by ≥ 1.5 g/dL · Relevant Reduction in units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk
Platelet Response (HI-P) (pre-treatment, <100 x 10 ⁹ /L)	· Absolute increase of $\geq 30 \times 10^9$/L for participants starting with $> 20 \times 10^9$/L platelets · Increase from $<20 \times 10^9$/L to $>20 \times 10^9$/L and by at least 100% ^b
Neutrophil Response (HI-N) (pretreatment, <1.0 x 10 ⁹ /L)	· At least 100% increase and an absolute increase $>0.5 \times 10^9$/L ^b
Progression or Relapse After HI ^c	At least 1 of the following: · At least 50% decrease from maximum response levels in granulocytes or platelets · Reduction in Hgb by ≥ 1.5 g/dL · Transfusion dependence

^a Pretreatment counts averages of at least 2 measurements (not influenced by transfusions, that is, no RBC transfusions for 2 weeks and no platelet transfusions for 1 week) ≥ 1 week apart (modification).

^b Modification to IWG (2000) response criteria.

^c 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 the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Notes:

Deletions to the IWG criteria are not shown. To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

The following trial-specific modifications will be applied: To accommodate the varying baseline transfusion burden of the subject population HI-E will be defined as follows:

- Subjects with baseline transfusion burden of < 4 pRBC units/8 weeks preceding first dose of investigational product: Hgb increase of ≥ 1.5 g/dL in the absence of transfusions.
- Subjects with baseline transfusion burden of ≥ 4 pRBC units/8 weeks: a relevant reduction of pRBC units by an absolute number of at least 4 pRBC units/8 weeks compared to the baseline transfusion burden in the 8 weeks preceding first dose of investigational product.

Source:([Cheson et al. 2006](#))

Table 16.g Altering Natural History of MDS According to IWG Criteria for MDS (Cheson, 2006)

Category	Response Criteria (responses must last at least 4 weeks)
Complete Remission ^c	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines ^a Persistent dysplasia will be noted ^{a,b} Peripheral blood ^c Hgb ≥ 11 g/dL Platelets ≥ 100 X 10 ⁹ /L Neutrophils ≥ 1.0 X 10 ⁹ /L ^b Blasts 0%
Partial Remission ^c	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pre-treatment but still > 5% Cellularity and morphology not relevant
Marrow CR ^{b,c}	Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pre-treatment ^b Peripheral blood: if HI responses, they will be noted in addition to marrow CR ^b
Stable Disease	Failure to achieve at least PR, but no evidence of progression for >8 wks
Failure ^c	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 pre-treatment
Relapse After CR or PR ^c	At least 1 of the following: Return to pre-treatment bone marrow blast percentage Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets ^c Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic Response ^c	Complete: Disappearance of the chromosomal abnormality without appearance of new ones Partial: At least 50% reduction of the chromosomal abnormality
Disease Progression	For subjects with: Less than 5% blasts: ≥50% increase in blasts to >5% blasts 5%-10% blasts: ≥50% increase to >10% blasts 10%-20% blasts: ≥50% increase to >20% blasts 20%-30% blasts ^d : ≥50% increase to >30% blasts Any of the following: ≥50% decrease from maximum remission/response in granulocytes or platelets ^c Reduction in Hgb by ≥2 g/ Transfusion dependence
Survival ^c	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

CONFIDENTIAL

Table 16.g Altering Natural History of MDS According to IWG Criteria for MDS (Cheson, 2006)

Category	Response Criteria (responses must last at least 4 weeks)
	Cause-specific death: death related to MDS

^a Dysplastic changes should consider the normal range of dysplastic changes (modification).

^b Modification to IWG (2000) response criteria.

^c Criteria not applicable for participants of this trial.

^d 20 – 30% blasts is considered AML according to WHO classification ([Vardiman et al. 2009](#)).

Notes: Deletions to IWG criteria are not shown. To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Source: ([Cheson et al. 2006](#)).

17.0 APPENDIX: GLOSSARY OF TERMS

17.1 Abbreviations

ADA	antidrug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BM	bone marrow
C	Cycle
CBC	complete blood count
CMH	Cochran-Mantel-Haenszel
CTCAE	Common Terminology Criteria for Adverse Events (National Cancer Institute)
CTR	Clinical Trial Regulation
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

EOT	end of trial
EOTx	end of treatment
EU	European Union
Eudra	European Union Drug Regulatory Authorities
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-An	Functional Assessment of Cancer Therapy-Anemia
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDF	growth differentiation factor
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HI-E	hematological improvement-erythroid
HRQoL	health-related quality of life
HTB	high transfusion burden
IA	interim analysis
IB	investigator's brochure
ICE	Intercurrent events
ICF	informed consent form (including electronic consent where applicable)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	independent data monitoring committee
IEC	independent ethics committee
IMiD	immunomodulatory drug
IMP	investigational medicinal product
INN	international nonproprietary name
INR	international normalized ratio
IPSS-M	Molecular International Prognostic Scoring System
IPSS-R	International Prognostic Scoring System - Revised
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IWG	international working group
LR-MDS	lower-risk myelodysplastic syndrome(s)
LTB	low transfusion burden
MDS	myelodysplastic syndrome(s)
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NTBI	non-transferrin-bound iron

PB	peripheral blood
PD	pharmacodynamic
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
POCBP	participant of childbearing potential
pRBC	packed red blood cells
PRCA	Pure Red Cell Aplasia
PROs	patient-reported outcomes
PT	Preferred Term
Q1W	every week
Q4W	every 4 weeks
QoL	quality of life
Q-TWiTR	quality-adjusted mean time without transfusion reliance
RBC	red blood cell
RBC-TI	red blood cell transfusion independence
RS	ring sideroblasts
RS-	RS negative
RS+	RS positive
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
sEPO	serum erythropoietin
SFU	safety follow-up
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TGF- β	transforming growth factor-beta
TPO	thrombopoietin
TSAT	transferrin saturation
TWiTR	mean time without transfusion reliance
ULN	upper limit of the normal
VAS	visual analogue scale
W	Week

17.2 Definitions

Hematologic improvement – erythroid response (HI-E) per IWG ([Cheson et al. 2006](#)) is defined as proportion of participants meeting HI-E criteria sustained over any consecutive 56-day period over the first 24 weeks from Week 1. Participants discontinued from the Treatment Period without achieving HI-E will be counted as nonresponders.

RBC-TI is defined as the absence of RBC transfusions for a prespecified period of time during continued treatment. The credibility of the data is dependent on the protocol specifying the minimal parameters for use of transfusions and documentation that the instructions were followed. Hence, an important supporting analysis would include an assessment of serial measurements of blood counts to ensure that the observed TI or RBC-TI was an actual treatment effect and not a bias in the administration of transfusions by the investigator.

AML: AML as per WHO classification of $\geq 20\%$ blasts in peripheral blood or bone marrow.

Progression to AML: time to AML progression is defined as the time between randomization and first diagnosis of AML as per WHO classification of $\geq 20\%$ blasts in peripheral blood or bone.

Evaluable Hgb values are the hemoglobin values collected ≤ 3 days prior to a RBC transfusion or collected >14 days after a transfusion. Exception if a participant is receiving RBC transfusions more frequently than every 14 days, the “pre-transfusion” value will be at least 7 days after RBC transfusion and prior to the subsequent transfusion. Available central laboratory results will be prioritized if hemoglobin values were reported on the same day by both central laboratory and local laboratory.

Baseline Hgb threshold will be the mean calculated by the sponsor using all evaluable Hgb values reported in the 8 weeks prior to randomization. At least 2 evaluable Hgb values should be available to calculate the baseline Hgb threshold. Available central laboratory results will be prioritized if hemoglobin values were reported on the same day by both central laboratory and local laboratory. This baseline Hgb threshold value will be provided to the investigator for each participant and this value will be used throughout the treatment period for assessment of transfusion requirement.

Concurrent mean Hgb increase will be calculated by the sponsor using all evaluable Hgb values during a 12-week period of transfusion independence. Available central laboratory results will be prioritized if hemoglobin values were reported on the same day by both central laboratory and local laboratory.

18.0 APPENDIX: REFERENCES

- Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., et al. 1993. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute*, 85(5), 365-76.
- Abel, G. A., Klepin, H. D., Magnavita, E. S., Jaung, T., Lu, W., Shallis, R. M., et al. 2021. Peri-transfusion quality-of-life assessment for patients with myelodysplastic syndromes. *Transfusion*, 61(10), 2830-6.
- Arber, D. A., Orazi, A., Hasserjian, R., Thiele, J., Borowitz, M. J., Le Beau, M. M., et al. 2016. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*, 127(20), 2391-405.
- Balducci, L. 2006. Transfusion independence in patients with myelodysplastic syndromes: impact on outcomes and quality of life. *Cancer*, 106(10), 2087-94.
- Bernard, E., Tuechler, H., Greenberg, P. L., Hasserjian, R. P., Arango Ossa, J. E., Nannya, Y., et al. 2022. Molecular international prognostic scoring system for myelodysplastic syndromes. *NEJM Evid*, 1(7), EVIDoa2200008.
- Blank, U. and Karlsson, S. 2011. The role of Smad signaling in hematopoiesis and translational hematology. *Leukemia*, 25(9), 1379-88.
- Bourke, S., Bennett, B., Oluboyede, Y., Li, T., Longworth, L., O'Sullivan, S. B., et al. 2024. Estimating the minimally important difference for the EQ-5D-5L and EORTC QLQ-C30 in cancer. *Health Qual Life Outcomes*, 22(1), 81.
- Brandenburg, N. A., Yu, R. and Revicki, D. A. 2010. Reliability and Validity of the FACT-AN In Patients with Low or Int-1-Risk Myelodysplastic Syndromes with Deletion 5q. *Blood*, 116(21), 3827.
- Brenet, F. and Scandura, J. M. 2015. Cutting the brakes on hematopoietic regeneration by blocking TGFbeta to limit chemotherapy-induced myelosuppression. *Mol Cell Oncol*, 2(3), e978703.
- Buckstein, R., Chodirker, L., Yee, K. W. L., Geddes, M., Leitch, H. A., Christou, G., et al. 2023. The burden of red blood cell transfusions in patients with lower-risk myelodysplastic syndromes and ring sideroblasts: an analysis of the prospective MDS-CAN registry. *Leuk Lymphoma*, 64(3), 651-61.
- Castelli, R., Delilieri, G. L., Colombo, R., Moreo, G., Gallipoli, P. and Pantaleo, G. 2014. Biosimilar epoetin in elderly patients with low-risk myelodysplastic syndromes improves anemia, quality of life, and brain function. *Ann Hematol*, 93(9), 1523-9.
- Cella, D. 1997. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. *Semin Hematol*, 34(3 Suppl 2), 13-9.
- Cella, D., Eton, D. T., Lai, J. S., Peterman, A. H. and Merkel, D. E. 2002. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *Journal of Pain & Symptom Management*, 24(6), 547-61.

- Cella, D. F., Tulsky, D. S., Gray, G., Sarafian, B., Linn, E., Bonomi, A., et al. 1993. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *Journal of Clinical Oncology*, 11(3), 570-9.
- Cheson, B. D., Greenberg, P. L., Bennett, J. M., Lowenberg, B., Wijermans, P. W., Nimer, S. D., et al. 2006. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*, 108(2), 419-25.
- Cocks, K. and Buchanan, J. 2023. How scoring limits the usability of minimal important differences (MIDs) as responder definition (RD): an exemplary demonstration using EORTC QLQ-C30 subscales. *Qual Life Res*, 32(5), 1247-53.
- Cocks, K., King, M. T., Velikova, G., de Castro, G., Jr., Martyn St-James, M., Fayers, P. M., et al. 2012. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Eur J Cancer*, 48(11), 1713-21.
- de Swart, L., Crouch, S., Hoeks, M., Smith, A., Langemeijer, S., Fenaux, P., et al. 2020. Impact of red blood cell transfusion dose density on progression-free survival in patients with lower-risk myelodysplastic syndromes. *Haematologica*, 105(3), 632-9.
- de Swart, L., Smith, A., Johnston, T. W., Haase, D., Droste, J., Fenaux, P., et al. 2015. Validation of the revised international prognostic scoring system (IPSS-R) in patients with lower-risk myelodysplastic syndromes: a report from the prospective European LeukaemiaNet MDS (EUMDS) registry. *Br J Haematol*, 170(3), 372-83.
- Delgado, C., Baweja, M., Crews, D. C., Eneanya, N. D., Gadegbeku, C. A., Inker, L. A., et al. 2021. A unifying approach for GFR estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. *J Am Soc Nephrol*, 32(12), 2994-3015.
- Della Porta, M. G., Garcia-Manero, G., Santini, V., Zeidan, A. M., Komrokji, R. S., Shortt, J., et al. 2024. Luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naïve, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): primary analysis of a phase 3, open-label, randomised, controlled trial. *Lancet Haematol*, 11(9), e646-e58.
- Diez-Campelo, M., Park, S., Iraca, T., Glassberg, M. B., DeCongelio, M., Bulkley, A., et al. 2024. The burden of transfusion dependence on caregivers of patients with lower-risk myelodysplastic syndromes in North America and Europe. *Blood*, 144(Supplement 1), 118-9.
- Efficace, F., Al Essa, W., Platzbecker, U., Niscola, P., Palumbo, G. A., Caocci, G., et al. 2023. Health-related Quality of Life Profile of Newly Diagnosed Patients With Myelodysplastic Syndromes by Age, Sex, and Risk Group: A Real-world Study by the GIMEMA. *Hemasphere*, 7(9), e944.
- Efficace, F., Cottone, F., Sommer, K., Kieffer, J., Aaronson, N., Fayers, P., et al. 2019. Validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Summary Score in patients with hematologic malignancies. *Value Health*, 22(11), 1303-10.

- Efficace, F., Niscola, P., Patriarca, A., Cottone, F., Palumbo, G. A., Caocci, G., et al. 2018. Pretreatment Health-Related Quality of Life Profile According to the EORTC QLQ-C30 in Patients with Myelodysplastic Syndromes (MDS): Analysis on 443 Lower-Risk MDS Patients. *Blood*, 132(Supplement 1), 2293.
- Fenaux, P., Haase, D., Santini, V., Sanz, G. F., Platzbecker, U., Mey, U., et al. 2021. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 32(2), 142-56.
- Fenaux, P., Platzbecker, U. and Ades, L. 2020. How we manage adults with myelodysplastic syndrome. *Br J Haematol*, 189(6), 1016-27.
- Fenaux, P., Santini, V., Spiriti, M. A. A., Giagounidis, A., Schlag, R., Radinoff, A., et al. 2018. A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin- α in anemic patients with low-risk MDS. *Leukemia*, 32(12), 2648-58.
- Gangat, N., Patnaik, M. M., Begna, K., Al-Kali, A., Litzow, M. R., Ketterling, R. P., et al. 2016. Survival trends in primary myelodysplastic syndromes: a comparative analysis of 1000 patients by year of diagnosis and treatment. *Blood Cancer J*, 6(4), e414.
- Gascón, P., Krendyukov, A., Mathieson, N. and Aapro, M. 2019. Epoetin alfa for the treatment of myelodysplastic syndrome-related anemia: A review of clinical data, clinical guidelines, and treatment protocols. *Leuk Res*, 81, 35-42.
- Gattermann, N. 2018. Iron overload in myelodysplastic syndromes (MDS). *Int J Hematol*, 107(1), 55-63.
- Germing, U., Oliva, E. N., Hiwase, D. and Almeida, A. 2019. Treatment of Anemia in Transfusion-Dependent and Non-Transfusion-Dependent Lower-Risk MDS: Current and Emerging Strategies. *Hemasphere*, 3(6), e314.
- Giagounidis, A., Arnan, M., Chee, L. C. Y., Cluzeau, T., Diez-Campelo, M., Hiwase, D., et al. 2024. Improvements in Hematological Parameters and Quality of Life (QOL) with Elritercept (KER-050): Results from an Ongoing Phase 2 Trial in Participants with Lower-Risk (LR) Myelodysplastic Neoplasms (MDS). *Blood*, 144(Supplement 1), 1825-6.
- Giesinger, J. M., La Nasa, G., Sparano, F., Angermeyer, M., Morelli, E., Mulas, O., et al. 2021. Health-related quality of life assessment in patients with myelodysplastic syndromes: Evidence from randomized clinical trials. *Clin Pract Epidemiol Ment Health*, 17(1), 307-14.
- Greenberg, P., Cox, C., LeBeau, M. M., Fenaux, P., Morel, P., Sanz, G., et al. 1997. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*, 89(6), 2079-88.
- Greenberg, P. L., Tuechler, H., Schanz, J., Sanz, G., Garcia-Manero, G., Sole, F., et al. 2012. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*, 120(12), 2454-65.
- Harnan, S., Ren, S., Gomersall, T., Everson-Hock, E. S., Sutton, A., Dhanasiri, S., et al. 2016. Association between transfusion status and overall survival in patients with myelodysplastic syndromes: a systematic literature review and meta-analysis. *Acta Haematol*, 136(1), 23-42.

- Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., et al. 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*, 20(10), 1727-36.
- Hinge, A. and Filippi, M. D. 2016. Deconstructing the complexity of TGFβ signaling in hematopoietic stem cells: Quiescence and beyond. *Curr Stem Cell Rep*, 2(4), 388-97.
- Jabbour, E., Kantarjian, H. M., Koller, C. and Taher, A. 2008. Red blood cell transfusions and iron overload in the treatment of patients with myelodysplastic syndromes. *Cancer*, 112(5), 1089-95.
- Jouzier, C., Cherait, A., Cony-Makhoul, P., Hamel, J. F., Veloso, M., Thepot, S., et al. 2022. Red blood cell transfusion burden in myelodysplastic syndromes (MDS) with ring Sideroblasts (RS): A retrospective multicenter study by the Groupe Francophone des Myélodysplasies (GFM). *Transfusion*, 62(5), 961-73.
- Kaka, S., Jahangirnia, A., Beauregard, N., Davis, A., Tinmouth, A. and Chin-Yee, N. 2022. Red blood cell transfusion in myelodysplastic syndromes: A systematic review. *Transfus Med*, 32(1), 3-23.
- Khoury, J. D., Solary, E., Ablu, O., Akkari, Y., Alaggio, R., Apperley, J. F., et al. 2022. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia*, 36(7), 1703-19.
- Kramer, H. J., Jaar, B. G., Choi, M. J., Palevsky, P. M., Vassalotti, J. A. and Rocco, M. V. 2022. An endorsement of the removal of race from GFR estimation equations: A position statement from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Kidney Dis*, 80(6), 691-6.
- Lewis, K., Williamson, M., Brown, E., Trenholm, E. and Hoge, C. 2024. Real-World Study of the Burden of Myelodysplastic Syndromes in Patients and Their Caregivers in Europe and the United States. *Oncol Ther*, 12(4), 753-74.
- Lucioni, C., Finelli, C., Mazzi, S. and Oliva, E. N. 2013. Costs and quality of life in patients with myelodysplastic syndromes. *Am J Blood Res*, 3(3), 246-59.
- Lyons, R. M., Foster, B., Jewett, A., Liu, L., Sen, R., Bui, C. N., et al. 2023. Psychometric validation and meaningful change threshold determination of EORTC QLQ-C30 physical functioning and Promis SF v1.0-Fatigue 7a functional domain in patients with high-risk myelodysplastic syndromes treated with venetoclax and azacitidine. *Blood*, 142(Suppl 1), 6472.
- Mađry, K., Lis, K., Fenaux, P., Bowen, D., Symeonidis, A., Mittelman, M., et al. 2023. Cause of death and excess mortality in patients with lower-risk myelodysplastic syndromes (MDS): A report from the European MDS registry. *Br J Haematol*, 200(4), 451-61.
- Malcovati, L., Della Porta, M. G. and Cazzola, M. 2006. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. *Haematologica*, 91(12), 1588-90.
- Malcovati, L., Della Porta, M. G., Strupp, C., Ambaglio, I., Kuendgen, A., Nachtigal, K., et al. 2011. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO classification-based Prognostic Scoring System (WPSS). *Haematologica*, 96(10), 1433-40.

- Malcovati, L., Hellstrom-Lindberg, E., Bowen, D., Ades, L., Cermak, J., Del Canizo, C., et al. 2013. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood*, 122(17), 2943-64.
- Massagué, J., Seoane, J. and Wotton, D. 2005. Smad transcription factors. *Genes Dev*, 19(23), 2783-810.
- Mesa, R. A., Talpaz, M., Mazerolle, F., Gorsh, B., M'Hari, M., Regnault, A., et al. 2025. Time Without Transfusion Reliance (TWiTR): Integrating survival quality into myelofibrosis treatment strategies based on the phase 3 SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM trials. *EJHaem*, 6(3), e70075.
- Nachtkamp, K., Stark, R., Strupp, C., Kündgen, A., Giagounidis, A., Aul, C., et al. 2016. Causes of death in 2877 patients with myelodysplastic syndromes. *Ann Hematol*, 95(6), 937-44.
- Oken, M. M., Creech, R. H., Tormey, D. C., Horton, J., Davis, T. E., McFadden, E. T., et al. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*, 5(6), 649-55.
- Oliva, E. N., Nobile, F., Alimena, G., Ronco, F., Specchia, G., Impera, S., et al. 2011a. Quality of life in elderly patients with acute myeloid leukemia: patients may be more accurate than physicians. *Haematologica*, 96(5), 696-702.
- Oliva, E. N., Platzbecker, U., Della Porta, M. G., Garcia-Manero, G., Santini, V., Fenaux, P., et al. 2024. Health-related quality of life of luspatercept versus epoetin alfa in red blood cell transfusion-dependent lower-risk myelodysplastic syndromes: Results from the final data cut of the phase 3 COMMANDS study. *Blood*, 144(Supplement 1), 3216-.
- Oliva, E. N., Platzbecker, U., Fenaux, P., Garcia-Manero, G., LeBlanc, T. W., Patel, B. J., et al. 2021. Targeting health-related quality of life in patients with myelodysplastic syndromes - current knowledge and lessons to be learned. *Blood Rev*, 100851.
- Oliva, E. N., Schey, C. and Hutchings, A. S. 2011b. A review of anemia as a cardiovascular risk factor in patients with myelodysplastic syndromes. *Am J Blood Res*, 1(2), 160-6.
- Papaemmanuil, E., Cazzola, M., Boulton, J., Malcovati, L., Vyas, P., Bowen, D., et al. 2011. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. *New England Journal of Medicine*, 365(15), 1384-95.
- Paulson, R. F., Shi, L. and Wu, D. C. 2011. Stress erythropoiesis: new signals and new stress progenitor cells. *Curr Opin Hematol*, 18(3), 139-45.
- Pickard, A., Neary, M. and Cella, D. 2007. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health and Quality of Life Outcomes*, 5(70), 1-8.
- Platzbecker, U. 2019. Treatment of MDS. *Blood*, 133(10), 1096-107.
- Platzbecker, U. 2020. New approaches for anemia in MDS. *Clin Lymphoma Myeloma Leuk*, 20 Suppl 1, S59-60.
- Platzbecker, U., Hofbauer, L. C., Ehninger, G. and Hölig, K. 2012. The clinical, quality of life, and economic consequences of chronic anemia and transfusion support in patients with myelodysplastic syndromes. *Leuk. Res*, 36(5), 525-36.
- Platzbecker, U., Santini, V., Fenaux, P., Sekeres, M. A., Savona, M. R., Madanat, Y. F., et al. 2024. Imetelstat in patients with lower-risk myelodysplastic syndromes who have

- relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*, 403(10423), 249-60.
- Pleyer, L., Heibl, S., Tinchon, C., Vallet, S., Schreder, M., Melchardt, T., et al. 2023. Health-related quality of life as assessed by the EQ-5D-5L predicts outcomes of patients treated with azacitidine-a prospective cohort study by the AGMT. *Cancers (Basel)*, 15(5).
- Regnault, A., Pompilus, F., Ciesluk, A., Mazerolle, F., Bejar, R., Fram, R. J., et al. 2021. Measuring patient-reported physical functioning and fatigue in myelodysplastic syndromes using a modular approach based on EORTC QLQ-C30. *J Patient Rep Outcomes*, 5(1), 60.
- Revicki, D. A., Brandenburg, N. A., Muus, P., Yu, R., Knight, R. and Fenaux, P. 2013. Health-related quality of life outcomes of lenalidomide in transfusion-dependent patients with Low- or Intermediate-1-risk myelodysplastic syndromes with a chromosome 5q deletion: results from a randomized clinical trial. *Leuk. Res*, 37(3), 259-65.
- Ryblom, H., Hast, R., Hellström-Lindberg, E., Winterling, J. and Johansson, E. 2015. Self-perception of symptoms of anemia and fatigue before and after blood transfusions in patients with myelodysplastic syndromes. *Eur J Oncol Nurs*, 19(2), 99-106.
- Schanz, J., Tuchler, H., Sole, F., Mallo, M., Luno, E., Cervera, J., et al. 2012. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. *Journal of Clinical Oncology*, 30(8), 820-9.
- Spiriti, M. A., Latagliata, R., Niscola, P., Cortelezzi, A., Francesconi, M., Ferrari, D., et al. 2005. Impact of a new dosing regimen of epoetin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome. *Ann Hematol*, 84(3), 167-76.
- Stauder, R., Lambert, J., Desruol-Allardin, S., Savre, I., Gaugler, L., Stojkov, I., et al. 2020. Patient-reported outcome measures in studies of myelodysplastic syndromes and acute myeloid leukemia: Literature review and landscape analysis. *Eur J Haematol*, 104(5), 476-87.
- Stojkov, I., Conrads-Frank, A., Rochau, U., Arvandi, M., Koinig, K. A., Schomaker, M., et al. 2023. Determinants of low health-related quality of life in patients with myelodysplastic syndromes: EUMDS Registry study. *Blood Adv*, 7(12), 2772-83.
- Tan, S., Chee, L., Ross, D., Cluzeau, T., Giagounidis, A., Valcárcel, D., et al. Activin A inhibition by elritercept (KER-050) is associated with evidence of cardiovascular benefit: Translation of preclinical observations to humans with MDS (P760). EHA 2024, 2024 Madrid, Spain.
- Trudeau, J. J., He, J., Rose, E., Panter, C., Randhawa, S. and Gater, A. 2020. Content validity of patient-reported outcomes for use in lower-risk myelodysplastic syndromes. *J Patient Rep Outcomes*, 4(1), 69.
- Valcárcel, D., Giagounidis, A., Chee, L., Ross, D., Bernal, T., Tan, S., et al. Reduced ferritin and increased bone specific alkaline phosphatase in participants with lower-risk MDS treated with elritercept (KER-050) support potential to rebalance the osteohematopoietic niche (S302). EHA 2024, 2024 Madrid, Spain.

- Vardiman, J. W., Thiele, J., Arber, D. A., Brunning, R. D., Borowitz, M. J., Porwit, A., et al. 2009. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*, 114(5), 937-51.
- Verma, A., Suragani, R. N., Aluri, S., Shah, N., Bhagat, T. D., Alexander, M. J., et al. 2020. Biological basis for efficacy of activin receptor ligand traps in myelodysplastic syndromes. *J Clin Invest*, 130(2), 582-9.
- Yamazaki, M., Fukushima, H., Shin, M., Katagiri, T., Doi, T., Takahashi, T., et al. 2009. Tumor necrosis factor alpha represses bone morphogenetic protein (BMP) signaling by interfering with the DNA binding of Smads through the activation of NF-kappaB. *J Biol Chem*, 284(51), 35987-95.
- Zeidner, J. F., Mazerolle, F., Norton, J., Regnault, A., Kristo, F., Romero, H., et al. 2023. Time without transfusion reliance: a novel patient-centric metric for new therapies in myelodysplastic syndromes. *Haematologica*, 108(4), 1196-9.
- Zingariello, M., Martelli, F., Ciaffoni, F., Masiello, F., Ghinassi, B., D'Amore, E., et al. 2013. Characterization of the TGF-beta1 signaling abnormalities in the Gata1^{low} mouse model of myelofibrosis. *Blood*, 121(17), 3345-63.

Signature Page for TAK-226-3001-Protocol

Title:

Approval Task	Xiaofei Zhou Xiaofei.Zhou@takeda.com Clinical 02-Sep-2025 19:00:22 GMT+0000
Approval Task	Alexander Vorog Alexander.Vorog@takeda.com Clinical 03-Sep-2025 14:26:44 GMT+0000
Approval Task	Meliessa Hennessy meliessa.hennessy@takeda.com Clinical 03-Sep-2025 16:02:10 GMT+0000
Approval Task	Cong Li Cong.Li@takeda.com Statistics 03-Sep-2025 17:50:15 GMT+0000

Document Number: TDN-000590999 v1.0