



GLOBAL INVESTIGATOR'S BROCHURE

Elritercept (TAK-226)

Edition 8, 01 July 2025 replacing Keros Edition 7, 29 July 2024

Safety Data Cutoff Date: 03 April 2025

Sponsor:

Takeda Development Center Americas, Inc.
500 Kendall Street
Cambridge, MA 02142 USA

CONFIDENTIAL INFORMATION

The information in this document is strictly confidential and should be available for review only by investigators, potential investigators, and specified institutional review boards/ethics committees. No disclosure of the information contained in this document should take place without written authorization from the sponsor, except to the extent necessary to obtain informed consent from potential study participants.

CONFIDENTIAL

ASSESSMENT OF SUBSTANTIALITY AND SUMMARY OF CHANGES FROM PREVIOUS EDITION

Assessment of Substantiality

Edition 8 of the Elritercept Investigator's Brochure (IB), updated since the previous IB Edition 7 (release date 29 July 2024), is considered a nonsubstantial modification. This assessment was made based on the following:

- There are no substantial changes to the RSI expectedness of SARs as shown in Section 6 Summary of Data and Guidance for the Investigator.
- The overall benefit-risk profile of elritercept has not changed as shown in Section 6, Summary of Data and Guidance for the Investigator.
- There are no significant new toxicological or pharmacological data.

Summary of Changes

Takeda entered into an Exclusive License Agreement with Keros Therapeutics, Inc., under which Takeda has an exclusive right to further develop, manufacture, and commercialize elritercept outside of mainland China, Hong Kong, and Macau. As a result, the IB was converted from a Keros Therapeutics, Inc to Takeda template. This involved sections being renamed and reordered throughout the document. The following table provides a guide to sections that have changed name and/or number between (Keros) IB Edition 7 and (Takeda) Edition 8.

IB Edition 7.0 Section	IB Edition 8.0 Section
1. SUMMARY	1.0 SUMMARY
1.1 Investigational Medicinal Product and Indication	1.1 Nonclinical Summary
1.2 Nonclinical Pharmacology	1.1.1 Nonclinical Pharmacology
1.3. Nonclinical Pharmacokinetics and Toxicokinetics	1.1.2 Nonclinical Pharmacokinetics and Toxicokinetics
1.4. Toxicology	1.1.3 Toxicology
1.5. Clinical Experience	1.2 Summary of Effects in Humans
2. INTRODUCTION	2.0 INTRODUCTION
2.1. Mechanism of Action	2.1 Mechanism of Action
2.2. Current Clinical Landscape	2.2 Disease Indications
2.2.1. Elritercept as a Potential Treatment for Anemia in Lower-Risk Myelodysplastic Syndromes	2.2.1. Elritercept as a Potential Treatment for Anemia in Lower-Risk Myelodysplastic Syndromes
2.2.2. Elritercept as a Potential Treatment for Myelofibrosis	2.2.2 Elritercept as a Potential Treatment for Myelofibrosis
3. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION	3.0 PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION
3.1. Pharmaceutical Presentation	3.1 Molecular Formula and Chemical Name
3.2. Physical and Chemical Properties of the Drug Substance	3.2 Physical, Chemical, and Pharmaceutical Properties
3.3. Formulation Including Excipients	3.3 Formulation

IB Edition 7.0 Section	IB Edition 8.0 Section
3.4.Storage, Handling, and Stability	
4. NONCLINICAL STUDIES	4.0 NONCLINICAL STUDIES
	4.1 Introduction
4.1. Nonclinical Pharmacology	4.2 Nonclinical Pharmacology
4.1.1. In Vitro Pharmacology Studies	4.2.1 Pharmacodynamic Activity Related to the Proposed Mechanism of Action
	4.2.1.1 In Vitro Pharmacology Potency and selectivity
4.1.2. In Vivo Pharmacology Studies	4.2.1.2 In Vivo Pharmacology Studies
4.2. Absorption and Pharmacokinetics	4.3 Nonclinical Pharmacokinetics and Product Metabolism
4.2.1. Single-Dose Pharmacokinetic Studies	
4.2.2. Toxicokinetics	
4.2.3. Metabolic Information	
4.3. TOXICOLOGY STUDIES	4.4 Toxicology
4.3.1. Sprague Dawley Rats	4.4.1 Repeat-Dose Studies
4.3.2. Cynomolgus Monkey (Non-human Primate)	
4.3.3. Carcinogenicity	4.4.3 Carcinogenicity
4.3.4. Development and Reproductive Toxicity	4.4.4 Reproductive Toxicity
4.3.5. Genotoxicity (Mutagenicity)	4.4.2 Genotoxicity (Mutagenicity)
4.3.6. Local Tolerance	4.4.5.1 Local Tolerance
5. EFFECTS IN HUMANS	5.0 EFFECTS IN HUMANS
5.1. OVERVIEW OF CLINICAL STUDIES	5.1 Overview of the Elritercept Clinical Program
5.1.1. Study KER-050-01: Completed – Phase 1, First-in-Human	5.1.1.1 Study KER-050-01: Completed – Phase 1, First-in-Human
5.1.2. Study KER050-MD-201: Ongoing – Phase 2	5.1.1.2 Study KER050-MD-201: Ongoing – Phase:2
5.1.3. Study KER050-MF-301: Ongoing – Phase 2	5.1.1.3 Study KER050-MF-301: Ongoing – Phase 2
5.1.4. Study KER-050-D301: Planned – Phase 3	Not Applicable
5.2. Safety in Clinical Studies	5.3 Clinical Safety
5.2.1. Study KER-050-01	5.3.1Study KER-050-01
5.2.2. Study KER050-MD-201	5.3.2 Study KER050-MD-201
5.2.3. Study KER050-MF-301	5.3.4 Study KER050-MF-301
5.2.4. Safety Conclusions	5.3.5 Safety Conclusions
5.3. Clinical Pharmacology	5.2 Clinical Pharmacology
5.3.1. Pharmacokinetics and Product Metabolism in Humans	5.2.1 Pharmacokinetics
5.3.2. Pharmacodynamics in Humans	5.2.2 Pharmacodynamics in Humans
5.4. Immunogenicity	5.2.3 Immunogenicity
5.4.1. Study KER-050-01	5.2.3.1 Study KER-050-01
5.4.2. Study KER050-MD-201	5.2.3.2 Study KER050-MD-201
5.4.3. Study KER050-MF-301	5.2.3.3 Study KER050-MF-301

IB Edition 7.0 Section	IB Edition 8.0 Section
5.5.EFFICACY	5.4 Clinical Efficacy
5.5.1. Study KER-050-01	
5.5.2. Study KER050-MD-201	Not Applicable
5.5.2.5. Pharmacodynamic Changes Related to Improvement of Anemia and Potential Effects Beyond Anemia in the MDS RP2D Population	5.2.2.2.1 Pharmacodynamic Changes Related to Improvement of Anemia and Potential Effects Beyond Anemia in the MDS RP2D Population
5.5.3. Study KER050-MF-301	Not Applicable
5.6. MARKETING EXPERIENCE	5.5 Marketing Experience
6. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR	6.0 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR
6.1. Posology and Method of Administration	6.2 Summary of Clinical Studies
6.2. Contraindications	6.7 Contraindications
6.3 Special Warnings and Special Precautions for Use	6.5 Special Warnings and Precautions for Use
6.4. Drug-Drug Interactions	6.8 Drug Interactions and Other Forms of Interactions
6.5. Use During Pregnancy and Lactation	6.9 Pregnancy and Lactation
6.6. Undesirable Effects	6.3 Potential Benefits
6.6.1. Potential Risks	6.4 Potential Risks of Elritercept Treatment
6.7. Overdose	6.10 Overdose
6.8. Pharmacokinetic Properties	6.2.1 Clinical Pharmacokinetics 6.2.2 Clinical Pharmacodynamics
6.9. NONCLINICAL TOXICOLOGY STUDIES	6.1 Summary of Nonclinical Studies
6.10. Drug Abuse and Dependency	6.11 Drug Abuse and Dependence
7. REFERENCE SAFETY INFORMATION	6.4.1 Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions
8. REFERENCES	7.0 REFERENCES
APPENDIX A SUMMARY OF TOXICOKINETIC DATA FROM COMPLETED TOXICOLOGY STUDIES	APPENDIX A SUMMARY OF TOXICOKINETIC DATA FROM COMPLETED TOXICOLOGY STUDIES
APPENDIX B ELRITERCEPT BINDING AFFINITY AND CELLULAR INHIBITION OF COMMERCIALY AVAILABLE TGF B SUPERFAMILY LIGANDS	Not applicable
APPENDIX C SUMMARY OF NONCLINICAL PHARMACOLOGY STUDIES OF ELRITERCEPT/RKER-050	APPENDIX B SUMMARY OF NONCLINICAL PHARMACOLOGY STUDIES OF ELRITERCEPT/RKER-050
APPENDIX D STUDY KER050-MF-301 BASE STUDY TABLES	APPENDIX C STUDY KER050-MF-301 BASE STUDY TABLES
APPENDIX E NARRATIVES FOR DEATHS	Not applicable
Not applicable indicates that content was not carried over from Edition 7 to Edition 8 (due to update during revision and/or in keeping with Takeda guidelines).	

The following information provides a high-level summary of the major changes to the previous IB Edition 7 (29 July 2024). Other changes in Edition 8 include updates to the List of

CONFIDENTIAL

Abbreviations and Terms, eliminating redundancy (Text and/or Tables) and editorial changes to confer brevity and improve clarity. Corrections of typographical errors, punctuation, grammar, terms and abbreviations, and formatting are not specifically listed.

Section	Title	Summary of Change
Global		Language/scope was updated to conform to Takeda style conventions/guidelines.
Cover Page		Address for Takeda provided.
Following Cover Page	ASSESSMENT OF SUBSTANTIALITY AND SUMMARY OF CHANGES FROM PREVIOUS EDITION	Statement that this IB update is considered a nonsubstantial modification and basis for this assessment (added per Takeda format/guidelines).
	Summary of Changes	Specified that IB Edition 8 was converted from a Keros Therapeutics, Inc. format to Takeda template.
1.0	SUMMARY	Summarized the terms of Takeda's Exclusive License Agreement with Keros Therapeutics, Inc.
1.2	Summary of Effects in humans	Summarized the clinical program of elritercept and clarified trials initiated by Keros Therapeutics, Inc. and clinical trial initiated by Hansoh (Shanghai) Healthcare Co., Ltd.
1.2.2	Elritercept in Lower-Risk Myelodysplastic Syndromes	Information added for Hansoh-initiated trial of elritercept in adults with anemia due to LR-MDS in mainland China (Study HS-20106).
2.2	Disease Indications (Formerly titled <i>Current Clinical Landscape</i>)	This section was made more concise, focusing the information provided on overviews of MDS and MF, brief statement on unmet need, and rationale for elritercept therapy for those disease indications.
3.3	Formulation/ Table 5.c	Information removed: • Process I (no longer used). • details on quality or quantitative composition in formulation.
4.0	NONCLINICAL STUDIES	Added report numbers for source documents.
4.2.1.1	In Vitro Pharmacology Potency and Selectivity	Removed Keros Therapeutics, Inc. Appendix B. ELRITERCEPT BINDING AFFINITY AND CELLULAR INHIBITION OF COMMERCIALY AVAILABLE TGF-B SUPERFAMILY LIGANDS. Table 28. The key ligand information was included in Table 4.a.
4.4.1	Repeat-Dose Studies	This section was streamlined and findings from the subchronic and chronic toxicity studies were presented. Removed summary of the 35-day rat study (Study 2697-005) and the 35-day NHP study (Study 2697-006).
5.0	EFFECTS IN HUMANS	Updated as of 03 April 2025 unless otherwise indicated.

Section	Title	Summary of Change
5.1	Overview of the Elritercept Clinical Program	Summarized the clinical program of elritercept and clarified trials initiated by Keros Therapeutics, Inc. and clinical trial initiated by Hansoh (Shanghai) Healthcare Co., Ltd. Updated as of 03 April 2025; added information regarding Hansoh-initiated trial in mainland China (Study HS-20106-201).
5.2	Clinical Pharmacology	This section was made more concise. Figures from Keros v7.0, Section 5.3.1. based on preliminary analyses were not carried over into IB Edition 8: [Keros IB v7.0 Figure 3] Population Serum Concentration of Elritercept Over Time. [Keros IB v7.0 Figure 4] Exposure-Response Plot for Mean Change in Hemoglobin 8 Weeks Pre- vs Post-Treatment.
5.2.2.2.1	Pharmacodynamic Changes Related to Improvement of Anemia and Potential Effects Beyond Anemia in the MDS RP2D Population	Updated Figure 5.a (formerly Figure 7) as of 03 April 2025 with data beyond Study Week 48.
5.3.2	Study KER050-MD-201	Updated safety information based on available data as of 03 April 2025.
5.3.3	Study HS-20106-201	New subsection for ongoing phase 2 trial in participants with LR-MDS, Study HS-20106-201.
5.3.4	Study KER050-MF-301	Updated safety information based on available data as of 03 April 2025.
5.4	Clinical Efficacy	This section was revised to present efficacy information only from the completed phase 1 trial, Study KER-050-01. Preliminary/draft efficacy data from ongoing trials, Study KER050-MD-201 and Study KER050-MF-301 were not carried over into IB Edition 8 per Takeda guidelines.
6.0	SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR	Added statement to emphasize that the updates contained in this IB (Edition 8) are considered nonsubstantial.
6.4.1 [formerly Section 7.]	RSI for Assessment of Expectedness of SARs.	Statements were added regarding the elritercept + ruxolitinib combination regimen and to emphasize that life-threatening or fatal adverse reactions are considered unexpected by the sponsor for expedited reporting of SUSARs.
6.9	Pregnancy and Lactation	Updated the time period for reporting pregnancies and suspected pregnancies for consistency as outlined in the study protocol(s).
Appendix B	SUMMARY OF NONCLINICAL PHARMACOLOGY STUDIES OF ELRITERCEPT/RKER-050	Updated results from Study Report KTX-314.

Section	Title	Summary of Change
Keros v7.0 Appendix B	ELRITERCEPT BINDING AFFINITY AND CELLULAR INHIBITION OF COMMERCIALLY AVAILABLE TGF-B SUPERFAMILY LIGANDS. Table 28.	Deleted; the key ligand information is included in Table 4.a.
Keros v7.0 Appendix E	APPENDIX E NARRATIVES FOR DEATHS	Deleted per Takeda guidelines.

TABLE OF CONTENTS

1.0	SUMMARY	16
1.1	Nonclinical Summary	16
1.1.1	Nonclinical Pharmacology	16
1.1.2	Nonclinical Pharmacokinetics and Toxicokinetics	16
1.1.3	Toxicology.....	17
1.2	Summary of Effects in Humans	17
1.2.1	Elritercept in Healthy Volunteers-----	17
1.2.2	Elritercept in Lower-Risk Myelodysplastic Syndromes.....	18
1.2.3	Elritercept in Myelofibrosis.....	18
2.0	INTRODUCTION	19
2.1	Mechanism of Action.....	19
2.2	Disease Indications	22
2.2.1	Elritercept as a Potential Treatment for Anemia in Lower-Risk MDS	22
2.2.2	Elritercept as a Potential Treatment for Myelofibrosis	24
3.0	PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION	25
3.1	Molecular Formula and Chemical Name	25
3.2	Physical, Chemical, and Pharmaceutical Properties	26
3.3	Formulation.....	26
4.0	NONCLINICAL STUDIES.....	27
4.1	Introduction.....	27
4.2	Nonclinical Pharmacology.....	27
4.2.1	Pharmacodynamic Activity Related to the Proposed Mechanism of Action	27
4.2.2	Safety Pharmacology.....	28
4.3	Nonclinical Pharmacokinetics and Product Metabolism	29
4.4	Toxicology	30
4.4.1	Repeat-Dose Studies.....	31
4.4.2	Genotoxicity (Mutagenicity)	33
4.4.3	Carcinogenicity.....	34
4.4.4	Reproductive Toxicity	34
4.4.5	Other Toxicity Studies.....	36
5.0	EFFECTS IN HUMANS	36
5.1	Overview of the Elritercept Clinical Program	36
5.1.1	Study Subjects	39

5.2	Clinical Pharmacology	42
5.2.1	Pharmacokinetics	42
5.2.2	Pharmacodynamics	46
5.2.3	Immunogenicity	51
5.3	Clinical Safety	53
5.3.1	Study KER-050-01	53
5.3.2	Study KER050-MD-201	54
5.3.3	Study HS-20106-201	64
5.3.4	Study KER050-MF-301	65
5.3.5	Safety Conclusions	73
5.4	Clinical Efficacy	75
5.5	Marketing Experience	76
6.0	SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR	76
6.1	Summary of Nonclinical Studies	76
6.2	Summary of Clinical Studies	76
6.2.1	Clinical Pharmacokinetics	77
6.2.2	Clinical Pharmacodynamics	77
6.2.3	Clinical Summary of Safety	78
6.3	Potential Benefits	78
6.4	Emerging Safety Information	79
6.4.1	RSI for Assessment of Expectedness of SARs	79
6.5	Special Warnings and Precautions for Use	79
6.6	Special Populations	80
6.7	Contraindications	80
6.8	Drug Interactions and Other Forms of Interactions	80
6.9	Pregnancy and Lactation	80
6.10	Overdose	81
6.11	Drug Abuse and Dependence	81
6.12	Pharmaceutical Particulars	81
7.0	REFERENCES	81

LIST OF IN-TEXT TABLES

Table 3.a	Elritercept Structure and Properties	25
Table 3.b	Physicochemical Properties of TAK-226 Drug Substance	26
Table 3.c	Elritercept Drug Product Formulations Including Excipients	26

Table 4.a	Elritercept Ligand Affinities (K_D) and Cellular Inhibition (IC_{50}) for Key TGF- β Superfamily Ligands	28
Table 4.b	Good Laboratory Practice Repeat-Dose Toxicology/Pharmacokinetics Studies with Elritercept.....	30
Table 5.a	Overview of Completed and Ongoing Keros-Initiated Elritercept Clinical Studies (as of 03 April 2025).....	37
Table 5.b	Summary of Key Serum Elritercept PK Parameters by Treatment – Part 1 (SAD) (PK Population; Study KER-050-01).....	43
Table 5.c	Summary of Day 1 and Day 29 Serum Elritercept PK Parameters by Treatment – Part 2 (MAD) (PK Population; Study KER-050-01)	43
Table 5.d	Average Change in Markers of Erythropoiesis Over the First 8 or 12 Weeks During the Study by Dose Level (Part 1 Dose Escalation, NTD Participants).....	49
Table 5.e	Overview of TEAEs – LTS (Safety Population; Study KER050-MD-201)	55
Table 5.f	TEAEs Reported in $\geq 10\%$ of Total Participants by Preferred Term in LTS (Safety Population, Study KER050-MD-201).....	56
Table 5.g	Treatment-Related TEAEs Reported in $\geq 1\%$ Participants of Total Participants by Preferred Term – LTS (Safety Population; Study KER050-MD-201)	57
Table 5.h	TEAEs Leading to Dose Interrupted by SOC and PT in LTS (Safety Population: Study KER50-MD-201)	59
Table 5.i	TEAEs Leading to Dose Reduced by SOC and PT in LTS (Safety Population: Study KER50-MD-201).....	61
Table 5.j	TEAEs Leading to Discontinuation of Investigational Medicinal Product by SOC and PT in LTS (Safety Population; Study KER50-MD-201)	62
Table 5.k	Overview of TEAEs (Study HS-20106-201).....	65
Table 5.l	TEAEs by Preferred Term (Study HS-20106-201)	65
Table 5.m	Overview of TEAEs in Monotherapy (Safety Population; Study KER050-MF-301).....	66
Table 5.n	Overview of TEAEs in Combination Therapy (Safety Population; Study KER050-MF-301).....	67
Table 5.o	TEAEs Reported in $\geq 10\%$ Participants by Preferred Term in Monotherapy (Safety Population; Study KER050-MF-301)	69
Table 5.p	TEAEs Reported in $\geq 10\%$ Participants by Preferred Term in Combination Therapy (Safety Population; Study KER050-MF-301)	69

LIST OF IN-TEXT FIGURES

Figure 2.a	Overview of Erythropoietic and Thrombopoietic Pathways	19
Figure 2.b	Balance in SMAD Signaling Key for Effective Hematopoiesis: Proposed Role of Elritercept in Rebalancing SMAD Signaling in MDS and MF	22

Figure 5.a	Hemoglobin (g/dL) Change from Baseline Over Time (MDS RP2D Population, LTB + NT Participants; Ongoing Study KER050-MD-201)	48
------------	--	----

LIST OF APPENDICES

Appendix A	SUMMARY OF TOXICOKINETIC DATA FROM COMPLETED TOXICOLOGY STUDIES	86
Appendix B	SUMMARY OF NONCLINICAL PHARMACOLOGY STUDIES OF ELRITERCEPT/RKER-050	92
Appendix C	STUDY KER050-MF-301 BASE STUDY TABLES	98

LIST OF TERMS AND ABBREVIATIONS

Abbreviation	Term
ActRIIA	activin receptor type IIA
ActRIIB-Fc	activin receptor type IIB receptor Fc fusion protein
ADA	anti-drug antibody (ies)
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC _{last}	area under the concentration-time curve calculated from time 0 (dosing) to the last quantifiable concentration
AUC _{0-inf}	area under the concentration-time curve calculated from time 0 (dosing) extrapolated to infinity
AUC _{0-Xhr}	area under the concentration-time curve calculated from time 0 (dosing) to X hours post-dose
Baso-E:	basophilic erythroblast;
BFU-E	burst forming unit-erythrocyte
BFU-MK	burst forming unit-megakaryocyte;
BID	twice a day
BIW	biweekly (twice every week)
BLQ	below the limit of quantification
BM	Bone marrow
BMP	bone morphogenetic protein
BSAP	bone-specific alkaline phosphatase
C1D1	Cycle 1 Day 1
CFU-E	colony forming unit-erythrocyte
CFU-MK	colony forming unit-megakaryocyte
CH2(3)	heavy chain constant region domain 2(3)
CHO	Chinese hamster ovary
CL	clearance
CL/F	apparent total body clearance from serum
C _{max}	maximum (peak) concentration
C _{min}	minimum observed serum concentration
CMMML	chronic myelomonocytic leukemia
C _{trough}	concentration prior to next dose
C _{troughSS}	C _{trough} at steady state
CTCAE	Common Terminology Criteria for Adverse Events;
CV	coefficient of variation
DCO	data cutoff
DIPSS	Dynamic International Prognostic Scoring System

Abbreviation	Term
DLT	dose-limiting toxicity
ECD	extracellular domain
ECG	electrocardiogram
EMA	European Medicines Agency
EPO	erythropoietin
Ery	erythroid
ESA	erythropoiesis-stimulating agent
ET	essential thrombocythemia
Fc	fragment crystallizable
FIH	first-in-human
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GATA-1	GATA binding protein 1, a.k.a. erythroid transcription factor
GD	Gestation Day
GDF	growth differentiation factor
GGG	glycine–glycine–glycine
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCT	hematocrit
HEK	human embryonic kidney
Hgb	hemoglobin
HI-E	hematological improvement-erythroid
HS-20106	elritercept (China)
HSPC	hematopoietic stem and progenitor cell
HTB	high transfusion burden
IB	Investigator's Brochure
IC ₅₀	half maximal inhibitory concentration
ICH	International Council for Harmonisation
IgG1	human immunoglobulin G1
IL	interleukin
INN	international nonproprietary name
IP	intraperitoneal
IPSS	International Prognostic Scoring System
IPSS-M	International Prognostic Scoring System - molecular prognostic model
IPSS-R	International Prognostic Scoring System-Revised
ISR	injection-site reaction
IWG	International Working Group
K _D	equilibrium dissociation constant
KER-050	elritercept
LR	lower-risk

Abbreviation	Term
LTB	low transfusion burden
LTE	Long-Term Extension
LTS	Long-Term Study
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDS	myelodysplastic syndromes or myelodysplastic neoplasms
MDX	mouse model of Duchenne muscular dystrophy
MF	myelofibrosis
NA	not applicable
NHP	non-human primate
NOAEL	no-observed-adverse-effect-level
NT	non-transfused
NTD	non-transfusion dependent
NT-proBNP	N-terminal pro b-type natriuretic peptide
OECD	Organisation for Economic Co-operation and Development
OHN	Oste hematopoietic niche
Ortho E	orthochromatic erythroblast
ORX	orchiectomized
PD	pharmacodynamic(s)
pEFD	preliminary embryo-fetal development
PK	pharmacokinetic(s)
PLT	platelet
PMF	primary myelofibrosis
PO	oral administration
Poly-E	polychromatic erythroblast
popPK	population pharmacokinetics
Pro-E	proerythroblast
PT	Preferred Term
PV	polycythemia vera
Q2W	every 2 weeks; dosed every other week
QTc	corrected QT interval
QTcF	Fridericia corrected QT interval
QW	(once) weekly
RAUC	AUC _{0-168hr Day 29 or 85} /AUC _{0-168hr Day 1}
RBC	red blood cell
RKER-050	research form of elritercept
RP2D	recommended Part 2 dose
RS	ring sideroblasts

Abbreviation	Term
RSI	reference safety information
Rux	ruxolitinib
SAD	single ascending dose
SAE	serious adverse event
SAR	serious adverse reaction
SC	subcutaneous(lee)
SMAD	mothers against decapentaplegic (a family of structurally similar proteins that are the main signal transducers for receptors of the TGF- β superfamily)
SOC	System Organ Class
SRC	Safety Review Committee
S-S	disulfide bond
sTfR	soluble transferrin receptor
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TAC	transverse aortic constriction
TD	transfusion dependent
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TGF- β	transforming growth factor-beta
TI	transfusion independence
TK	toxicokinetic(s)
T_{oast}	time after dosing at which the last quantifiable concentration was observed
T_{max}	time to maximum observed concentration
US	United States
USAN	United States Adopted Name.
Veh	vehicle
$V_{az/F}$	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WT:	wild-type

1.0 SUMMARY

Under the terms of Takeda's Exclusive License Agreement with Keros Therapeutics, Inc., Takeda holds the rights to develop, commercialize, and manufacture elritercept (known as TAK-226; KER-050; HS-20106) outside of mainland China, Hong Kong, and Macau. Takeda is developing elritercept for the potential treatment of anemia in adults with very low-, low-, or intermediate-risk (lower-risk: [LR]) MDS; more recently defined as myelodysplastic neoplasms) and for the potential treatment of anemia in adults with myelofibrosis.

An overview of the elritercept clinical program is provided in Section 5.1.

Elritercept is a modified ActRIIA ligand trap that is designed to inhibit aberrant signaling by select TGF- β superfamily ligands, including activin A, activin B, GDF8 and GDF11 observed in diseases of ineffective hematopoiesis. This inhibition is expected to stimulate maturation and differentiation of early- and late-stage erythroid and megakaryocyte precursors in the bone marrow, potentially restoring effective hematopoiesis.

Elritercept is produced under GMP in CHO cells and purified from the conditioned medium through a series of downstream processing steps including column chromatography, ultrafiltration, and nanofiltration. The drug product (Solution for Injection) is for SC administration.

Elritercept, formerly known as KER-050 and the research form of elritercept, referred to as RKER-050, are discussed throughout this document. Details on the difference between elritercept and RKER-050 are described further in Section 4.2. Clinical information for the ongoing studies KER050-MD-201 and KER050-MF-301 is as of 03 April 2025 (unless otherwise noted) and is presented in Section 5.0.

1.1 Nonclinical Summary

1.1.1 Nonclinical Pharmacology

In vitro pharmacology studies determined that elritercept is a potent binder and inhibitor of activin A, activin B, GDF8, and GDF11. Binding of multiple ligands within this pathway drives elritercept pharmacological effect. In vivo pharmacology studies in healthy wild-type mice and rodent disease models have demonstrated that elritercept potently induces erythropoiesis, increases platelet counts, has the potential to improve left ventricular function, increases muscle and bone mass, and prevents fibrosis.

1.1.2 Nonclinical Pharmacokinetics and Toxicokinetics

Single-dose PK studies conducted in Sprague Dawley rats and NHPs (cynomolgus monkeys) demonstrated that elritercept had low CL, low volume of distribution, and a long terminal elimination half-life $t_{1/2}$). Repeat-dose TK in NHPs resulted in exposures that were approximately dose-proportional with no difference between sexes, and the presence of ADA was limited to 3 (of 108) animals, which appeared to impact systemic exposure to elritercept in only 2 of the animals (1.9% total). In rats, however, repeat-dose TK resulted in exposures that were not

dose-proportional following repeat administration because of significant reductions in exposure from high levels of ADAs.

1.1.3 Toxicology

Key findings in the nonclinical GLP toxicity studies included mortality (rat, 3-month study, high dose only) and effects on kidney (rats and NHPs), adrenal glands (rats), bone (rats), liver (rats), salivary glands (NHPs), reproductive tissues (rats and NHPs) and increases in red cell mass (rats and NHPs). The majority of these key findings were observed in the high-dose groups and were reversible. Exceptions included changes in reproductive tissues that were not limited to the high-dose group and adrenal changes in rats, which trended toward reversibility but were not fully reversible. In addition, results from a developmental toxicity rat study indicate the potential for embryo-fetal toxicity. In a rat fertility study, there was prolongation of the estrous cycle, though there were no direct effects on female or male fertility.

1.2 Summary of Effects in Humans

The clinical program of elritercept includes 4 clinical trials initiated by Keros Therapeutics, Inc. (hereafter referred to as Keros) and 1 clinical trial initiated by Hansoh (Shanghai) Healthcare Co., Ltd (hereafter referred to as Hansoh).

To date, Keros-initiated trials include one completed phase 1 clinical trial in healthy participants, 2 ongoing phase 2 clinical trials in participants with LR-MDS and MF, respectively, and 1 ongoing phase 3 clinical trial in participants with LR-MDS. Hansoh, a licensing partner with Keros for elritercept solely in the territory of mainland China, Hong Kong, and Macau, has initiated a phase 2 clinical trial of elritercept in adults with anemia due to LR-MDS in the territory of mainland China.

An overview of the elritercept clinical program is provided in Section [5.1](#)

1.2.1 Elritercept in Healthy Volunteers-----

A FIH phase 1 trial (Study KER-050-01) has been completed in 48 healthy postmenopausal women, 38 of whom received ≥ 1 dose of elritercept and 10 of whom received placebo.

In this trial, elritercept was well tolerated at dose levels ranging from 0.05 to 4.5 mg/kg, the highest dose level tested. The most common TEAEs ($\geq 10\%$ participants) by the MedDRA PT following elritercept administration included haemoglobin increased and headache (31.6% each), and hypertension, nausea, and upper respiratory tract infection (10.5% each). All TEAEs reported following administration of elritercept were mild or moderate in severity and there were no TESAEs in participants following elritercept administration.

Serum elritercept exposure was dose-proportional following single SC doses ranging from 0.05 to 4.5 mg/kg. Absorption was slow, with median time to maximum observed concentration (T_{max}) of approximately 4.5 to 6 days, and mean $t_{1/2}$ of approximately 12 days. No accumulation was observed following 2 SC doses of 0.75 mg/kg administered 4 weeks apart.

Elritercept elicited dose-dependent increases in Hgb, reticulocytes, and RBCs. Decreases in FSH concentration, a marker of activin inhibition, as well as increases in BSAP were also observed following elritercept administration.

Further details regarding this trial can be found in Section [5.3.1](#).

1.2.2 Elritercept in Lower-Risk Myelodysplastic Syndromes

A phase 2 trial of elritercept in LR-MDS (Study KER050-MD-201) was initiated in 2020 and is currently ongoing as of the 03 April 2025 DCO date. Elritercept has been well tolerated without any DLTs at dose levels ranging from 0.75 to 5.0 mg/kg administered SC once every 28 days (Q4W). The most frequently reported ($\geq 15\%$ participants) TEAEs by MedDRA PT included diarrhoea (30 participants, 27.5%), fatigue (29 participants, 26.6%), COVID-19 (23 participants, 21.1%), anaemia (21 participants, 19.3%), dizziness, epistaxis, nausea, (19 participants, 17.4% each), dyspnoea (18 participants, 16.5%), and constipation, fall, and oedema peripheral, (17 participants, 15.6% each).

Elritercept treatment resulted in sustained increases in Hgb and reductions in transfusion burden. Corresponding improvements in QoL were observed. Additionally, changes in biomarkers of iron homeostasis and iron overload (ferritin), osteoblast activity (BSAP), thrombopoiesis (platelets), and cardiac stress (N-terminal prohormone of brain natriuretic protein [NT-proBNP]) support the potential of elritercept to address multiple aspects of MDS pathogenesis beyond anemia.

Further details regarding Study KER050-MD-201 can be found in Section [5.3.2](#).

In addition, Hansoh, who is a licensing partner with Keros for elritercept, known as “HS-20106” in this trial, has initiated a phase 2 clinical trial of elritercept in adults with anemia due to LR-MDS (Study HS-20106-201) in the territory of mainland China. Overall, 6 (54.5%) participants have experienced ≥ 1 TEAE, with only influenza-like illness, platelet count decreased, and white blood cell count reported for ≥ 2 participants.

Further details regarding Study HS-20106-201 can be found in Section [5.3.3](#).

1.2.3 Elritercept in Myelofibrosis

A phase 2 trial of elritercept in MF (Study KER050-MF-301) was initiated in 2021 and is ongoing as of the 03 April 2025 DCO date. Elritercept has been generally well tolerated as monotherapy and in combination with ruxolitinib at dose levels 0.75 mg/kg, 1.5 mg/kg, 3.0 mg/kg, 3.75 mg/kg, 4.5 mg/kg, and 5.0 mg/kg SC Q4W. After completion of Part 1, the recommended Part 2 dose (RP2D) was defined as 3.75 mg/kg every 4 weeks starting dose, with the option to up-titrate to 5.0 mg/kg every 4 weeks for insufficient response. The dose may also be reduced to 2.5 mg/kg every 4 weeks or 1.5 mg/kg every 4 weeks per the dose modification guidelines.

The most frequently reported ($\geq 15\%$ participants) TEAEs by MedDRA PT for participants with MF receiving elritercept as monotherapy included thrombocytopenia (11 participants, 30.6%), diarrhoea (9 participants, 25.0%), pyrexia (8 participants, 22.2%), asthenia, headache, and

hypertension (5 participants, 13.9% each). The most frequently reported ($\geq 15\%$ participants) TEAEs by MedDRA PT for participants with MF receiving elritercept in combination with ruxolitinib included diarrhoea (15 participants, 25.9%), anaemia (10 participants, 17.2%), and thrombocytopenia (9 participants, 15.5 %).

Preliminary PD data in Study KER050-MF-301 revealed potential for elritercept to improve anemia based on dose-dependent increases in markers of erythropoiesis, sustained increases in Hgb observed in both monotherapy and combination treatment arms, and reductions in transfusion burden, as monotherapy and in combination with ruxolitinib.

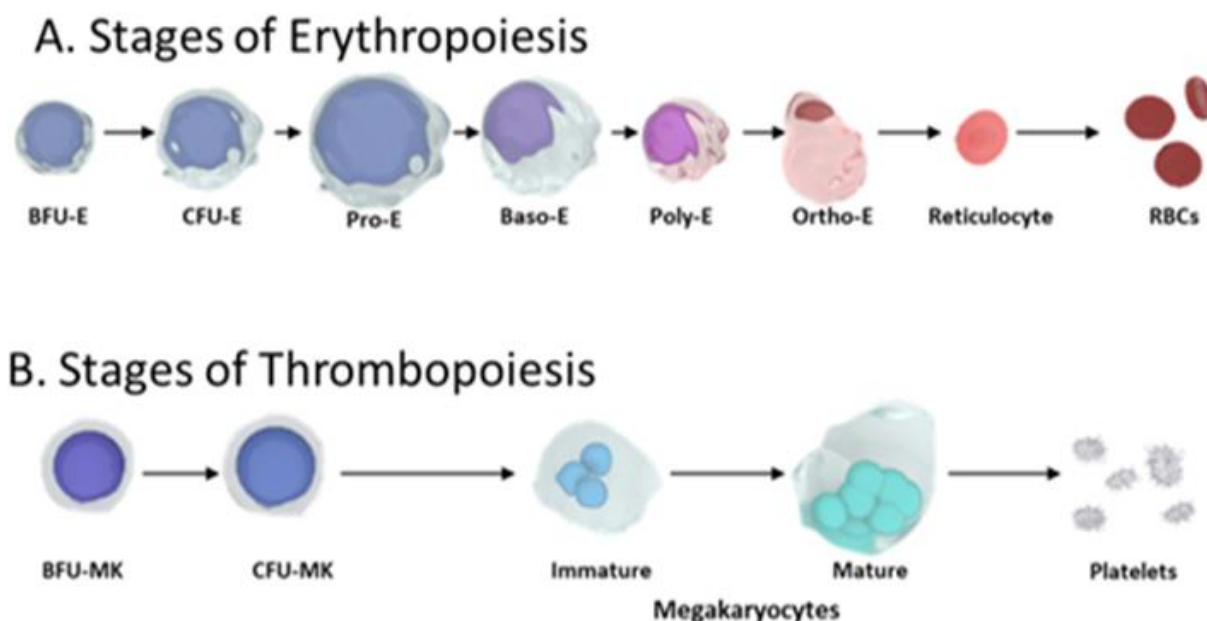
Further details regarding Study KER050-MF-301 can be found in Section 5.3.4.

2.0 INTRODUCTION

2.1 Mechanism of Action

Elritercept is designed to alter TGF- β signaling pathways at multiple stages of hematopoietic differentiation in both erythropoiesis and thrombopoiesis (Figure 2.a). Elritercept mediated inhibition of TGF- β superfamily ligands results in maturation and differentiation of early- and late-stage erythroid and megakaryocyte precursors in the bone marrow, thereby providing the potential to restore effective hematopoiesis.

Figure 2.a Overview of Erythropoietic and Thrombopoietic Pathways



The TGF- β superfamily comprises >30 ligands, which can be broadly grouped into subfamilies, including TGF- β s, activins, GDFs, and BMPs. The signaling of TGF- β superfamily ligands occurs via the SMAD family of proteins and, in general, TGF- β superfamily ligands act through

1 of 2 canonical pathways, SMAD1/5/9 or SMAD2/3. Activation of one pathway leads to the suppression of the other as a result of shared co-SMADs ([Ning et al. 2019](#); [Yamazaki et al. 2009](#)).

The TGF- β superfamily plays a key role in regulating hematopoiesis ([Söderberg et al. 2009](#)). The BMP family predominately signals through SMAD1/5/9, resulting in a PR erythropoiesis signal ([Blank and Karlsson 2011](#); [Massagué et al. 2005](#); [Paulson et al. 2011](#)).

In contrast, signaling through SMAD2/3 induces quiescence, self-renewal, and reduced hematopoietic maturation, where progenitor cells are stopped from progressing through later stages of hematopoiesis ([Brenet et al. 2013](#); [Brenet and Scandura 2015](#); [Hinge and Filippi 2016](#); [Yamazaki et al. 2009](#)) (Figure 2.b, left panel).

Activins and GDF ligands signal through SMAD2/3, thereby resulting in quiescence, and inhibition of these ligands has been found to reduce aberrant signaling through SMAD2/3 and enhance hematopoiesis ([Sako et al. 2010](#); [Suragani et al. 2014](#); [Verma et al. 2020](#)) (Figure 2.b, left panel).

Aberrations in the interaction between osteoblastic precursors and HSPCs within the bone marrow microenvironment can also perturb bone marrow niche biology and play a role in inducing or advancing disease. Perturbation of molecular signaling pathways, including TGF- β ligands, within the OHN contributes to ineffective hematopoiesis and cytopenias, as well as the development of an abnormal bone marrow microenvironment that allows for clonal hematopoiesis and eventual leukemic transformation ([Mies et al. 2016](#)).

The TGF- β ligand activin A is thought to be a key mediator in the maintenance of an OHN supportive of hematopoiesis, and overactive activin A signaling has been associated with pathogenesis of bone marrow disorders ([Raaijmakers 2012](#)). Moreover, multiple lines of evidence suggest that overactive activin A signaling contributes to the pathophysiology of MDS ([Verma et al. 2020](#)):

- Activin A is an inflammatory mediator ([Phillips et al. 2009](#)), and elevated levels in the bone marrow have been associated with increased fibrosis in hematologic disease ([Rambaldi et al. 2021](#)).
- Activin A stimulates osteoclast activity and inhibits osteoblast activity ([Fuller et al. 2000](#); [Pearsall et al. 2008](#)).
- Activin A signaling may alter the interface between bone progenitors and HSPCs within the OHN, thereby contributing to the pathophysiology of MDS ([Weidner et al. 2017](#)) and MF ([Rambaldi et al. 2021](#)).
- Elevated activin A levels have been observed with hematologic malignancies and activin A has been shown to promote malignant cell migration for both solid tumors and hematologic malignancies ([Portale et al. 2019](#); [Terpos et al. 2012](#)).

Thus, activin A represents a potential therapeutic target for the treatment of anemia in patients with LR-MDS.

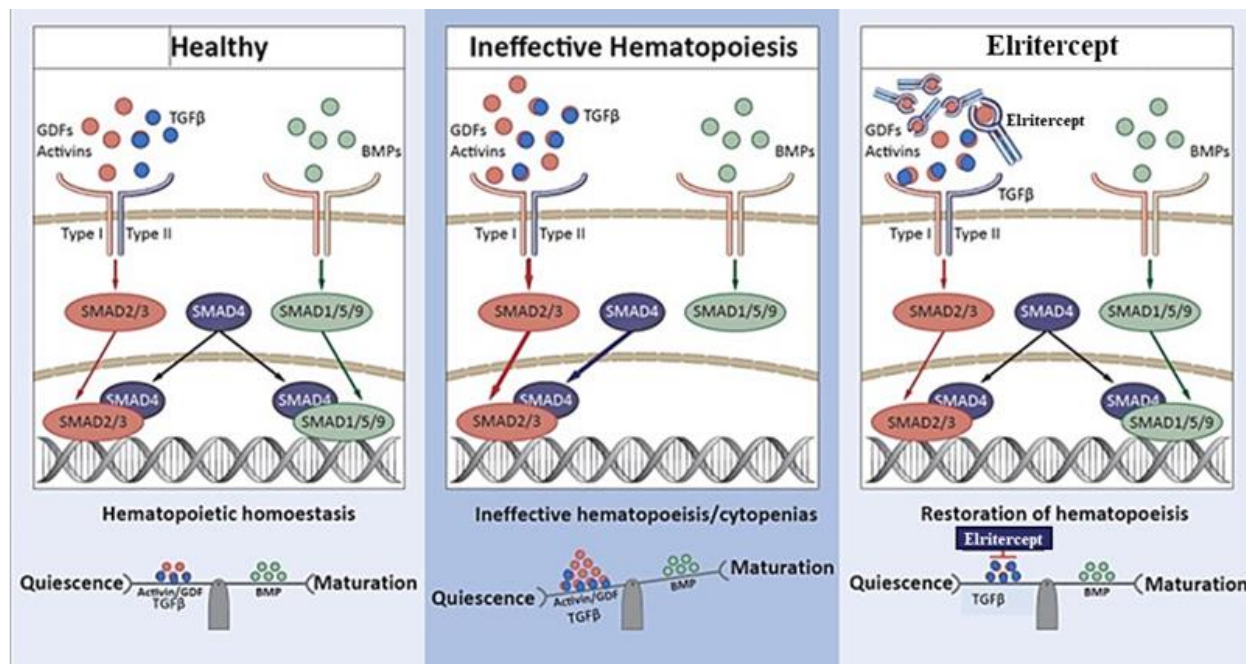
Imbalance between the SMAD2/3 and SMAD1/5/9 signaling, as a result of aberrant signaling by different TGF- β superfamily ligands in erythrocytes and megakaryocytes, can lead to ineffective hematopoiesis as observed in patients with MDS and MF ([Bewersdorf and Zeidan 2019](#); [Zingariello et al. 2013](#)) (Figure 2.b, middle panel]). Pharmacological inhibition of activins and GDFs to reduce SMAD2/3 activity may override aberrant TGF- β signaling and promote healthy hematopoiesis in patients with MDS and MF.

ActRIIA and ActRIIB are type II transmembrane receptors for TGF- β superfamily members, including GDFs and activins, that are involved in the negative regulation of hematopoiesis, skeletal muscle mass, and bone formation ([Lodberg 2021](#)). Elritercept comprises a modified sequence of the ECD of ActRIIA fused to the Fc region of IgG1. Elritercept is being developed as a therapeutic for cytopenias arising from ineffective hematopoiesis.

Elritercept functions as a ligand trap, binding and inhibiting the function of ligands that signal through SMAD2/3, including activin A, activin B, GDF8, and GDF11. By binding these ligands, elritercept is designed to rebalance SMAD signaling and to alter TGF- β signaling pathways at multiple stages of hematopoietic differentiation in both erythropoiesis (Figure 2.a) and thrombopoiesis (Figure 2.a). As such, elritercept-mediated inhibition of TGF- β superfamily ligands results in maturation and differentiation of early- and late-stage erythroid and megakaryocyte precursors in the bone marrow, providing the potential to restore effective hematopoiesis in patients with MDS and MF.

In addition, as detailed above, elritercept has potential to provide clinical benefits beyond the treatment of ineffective hematopoiesis through inhibition of activin A; these benefits may include impact on inflammation, bone metabolism, fibrosis, cardiac strain, and quality of life.

Figure 2.b Balance in SMAD Signaling Key for Effective Hematopoiesis: Proposed Role of Elritercept in Rebalancing SMAD Signaling in MDS and MF



2.2 Disease Indications

2.2.1 Elritercept as a Potential Treatment for Anemia in Lower-Risk MDS

2.2.1.1 Overview of MDS

MDS is a group of highly heterogeneous diseases characterized by ineffective hematopoiesis, often with a dramatic expansion of progenitor cells that are unable to mature into functioning cells, as well as cytopenias and morphologic dysplasia. MDS has also recently referred to as “myelodysplastic neoplasms” by the WHO ([Arber et al. 2016](#); [Khoury et al. 2022](#)). MDS is a rare condition that predominately affects older adults, with a median age at diagnosis of approximately 70 years.

The diagnosis of MDS is informed by a detailed medical history, thorough physical examination to identify cytopenia-related signs and symptoms, and assessment of blood and bone marrow ([Kasprzak et al. 2021](#)). MDS is traditionally classified according to the WHO criteria, with WHO 2016 ([Arber et al. 2016](#)) criteria basing classification on bone marrow morphology and WHO 5th Edition ([Khoury et al. 2022](#)) incorporating molecular data into the classification schema. For therapeutic purposes, prognosis is defined by universally accepted and validated IPSS criteria, with IPSS-R ([Greenberg et al. 2012](#)) being based on the percentage of marrow blasts, number and extent of blood cytopenias, and marrow cell karyotype, as well as IPSS-M ([Bernard et al. 2022](#)) being based on similar criteria plus molecular data. While recent updates to

WHO criteria and IPSS prognostic categorizations represent important developments in the field, current understanding of MDS is largely rooted in analyses using WHO 2016 and IPSS-R.

Patients with MDS are stratified into 5 risk groups using IPSS-R: very low-, low-, intermediate-, high-, and very high-risk MDS ([Fenaux et al. 2021](#); [Greenberg et al. 2012](#)). The frequencies of each IPSS-R risk group cohort have been estimated at <5% for very low risk, 65% to 75% for low risk, 15% to 20% for intermediate risk, 5% for high risk, and 5% to 10% for very high risk ([Li et al. 2022](#)). Cases of very low, low, or intermediate disease with the corresponding IPSS-R score of ≤ 4.5 points are considered LR-MDS ([Greenberg et al. 2012](#)). Patients with LR-MDS can be further subdivided according to morphologic, cytogenetic, and clinical characteristics, including the presence of deletion on chromosome 5q, namely del(5q), presence or absence of ring sideroblasts, predominant thrombocytopenia, hypoplastic MDS, and a large cluster of patients presenting with predominant anemia ([Fenaux et al. 2021](#); [Giagounidis and Haase 2020](#)).

MDS carries an increased risk of progression to AML ([Arber et al. 2016](#)) and approximately 30% of patients with MDS eventually progress to a diagnosis of AML ([Menssen and Walter 2020](#)); however, most patients with LR-MDS die of other causes (for example, infections, hemorrhage, or cardiovascular events before the disease progresses to AML) ([Dayyani et al. 2010](#); [Greenberg et al. 2012](#)).

A number of international and national evidence-based guidelines have been developed and are instrumental in MDS clinical decision-making, which remains challenging in a mostly elderly and heterogenous patient population ([Blum and Malcovati 2021](#); [Fenaux et al. 2021](#); [Kasprzak et al. 2021](#)). Treatment modalities for patients with LR-MDS remain limited.

Unmet need remains for a treatment that is efficacious with a durable response in a broad patient population, including difficult-to-treat patients with HTB. Patients with LR-MDS would benefit from a treatment that addresses not only MDS-associated anemia, but also addresses the resulting complication of iron overload, which itself impacts overall survival and prognosis. Therefore, the need remains for new treatment options that can effectively treat anemia at its source by improving erythropoiesis and iron utilization, along with reducing transfusion burden.

2.2.1.2 *Rationale for Elritercept Therapy for Lower-Risk Myelodysplastic Syndromes*

Cytopenias are common manifestations in patients with LR-MDS. Elritercept is designed to alter TGF- β signaling pathways at multiple stages of hematopoietic differentiation in both RBC and platelet precursors. Consequently, elritercept has the potential to provide therapeutic benefit in a broad subset of patients with LR-MDS who collectively have varying defects in commitment, differentiation, and maturation of multiple hematopoietic lineages; this could be important for patients with non-RS disease where terminal maturation agents such as lusparcept are ineffective, multilineage dysplasia where anemia and thrombocytopenia can co-occur, and HTB where multiple defects in the development pathway may exist in a single patient.

2.2.2 Elritercept as a Potential Treatment for Myelofibrosis

2.2.2.1 Overview of MF

MF is a myeloproliferative neoplasm characterized by bone marrow inflammation, clonal proliferation of myeloid cells, and megakaryocytic hyperplasia/dysplasia. MF exhibits substantial clinical heterogeneity and complex multifaceted biology. Abnormal interactions between aberrant megakaryocytes, osteoblasts, endothelium, stromal cells, hematopoietic stem cells, and myofibroblasts within the bone marrow, collectively contribute to bone marrow fibrosis, osteosclerosis, extramedullary hematopoiesis, and clonal proliferation ([Gangat and Tefferi 2020](#)).

At presentation, 70% to 85% of patients with MF are symptomatic from a generalized inflammatory milieu causing severe fatigue and constitutional symptoms such as fevers, night sweats, and bone pain. Patients may also have splenomegaly-associated symptoms, including abdominal symptoms and early satiety ([Smith et al. 1990](#)). Patients often experience multiple disease-associated and treatment-emergent cytopenias, including anemia and thrombocytopenia. Anemia in MF can impair quality of life, and may cause fatigue, weakness, exercise intolerance, angina, dizziness, cognitive impairment, or a diminished sense of well-being.

MF can arise de novo ([PMF]), evolve from underlying PV or essential ET, or arise as a secondary disorder from toxic exposures, MDS, lupus, and other conditions) ([Moulard et al. 2014](#)). PMF, post-PV MF, and post-ET MF have overlapping features and are all associated with JAK2, CALR, and MPL driver mutations ([Barbui et al. 2018](#)). PMF, PV, and ET remain distinct entities in WHO classification systems ([Arber et al. 2016](#); [Khoury et al. 2022](#)). Moreover, because of differing natural history ([Barbui et al. 2018](#)), WHO diagnostic and classification criteria employ a combination of major and minor features incorporating molecular, histologic, and hematology data to differentiate these similar conditions; significant updates made in the 2016 WHO classification ([Arber et al. 2016](#)) remain largely unchanged in the 2022 version.

The prognosis of MF varies based on etiology and several disease-related factors. For PMF, several diagnostic risk stratification tools have been proposed ([Gangat et al. 2011](#); [Tefferi 2021](#)). The DIPSS for PMF is well-known and utilized data on age, symptoms, and hematology to predict survival ([Kuykendall et al. 2019](#)). Criteria were later revised creating DIPSS Plus, which incorporates cytogenetic abnormalities and more data on hematology into the risk stratification algorithm ([Tefferi et al. 2018](#)). Since then, several models have attempted to incorporate more molecular data ([Kuykendall et al. 2019](#)) culminating in a genetically inspired GIPSS incorporating only genetic inputs to risk stratify ([Cervantes et al. 2009](#)). The lack of overlap among prognostic variables used in each model complicates risk stratification in PMF, but one analysis demonstrated that GIPSS outperforms DIPSS in predicting survival ([Gangat et al. 2011](#)).

Patients with PMF have reduced survival and succumb to leukemic transformation, progression of their disease, thrombosis and cardiovascular complications, infection, bleeding, portal hypertension, and secondary malignancies ([Cervantes et al. 2009](#)).

There remains significant unmet need for patients with MF, including a need for therapies to address MF-associated and treatment-associated anemia and thrombocytopenia. In addition,

there are currently no available therapies that treat the underlying pathophysiology including aberrant inflammatory signaling and bone marrow fibrosis.

2.2.2.2 Rationale for Elritercept Therapy for MF

In MF, inflammation and fibrosis caused by unrestrained proliferation of megakaryocyte precursors leads to ineffective hematopoiesis and cytopenias, contributing to poor prognosis and reduced survival for patients. By targeting imbalanced signaling of TGF-β superfamily ligands, elritercept has the potential to address ineffective hematopoiesis and treat cytopenias, not only by directly promoting maturation and differentiation of healthy hematopoietic precursors, but also by restoring balance in TGF-β superfamily signaling in the OHN making it more conducive to functional hematopoiesis. Treatment-related cytopenias are one of the factors limiting the clinical utility of treatments such as ruxolitinib that improve splenomegaly and constitutional symptoms in MF. By restoring erythropoiesis and thrombopoiesis, elritercept has potential to mitigate these cytopenias, as well as the potential to improve tolerability to ruxolitinib when administered in combination.

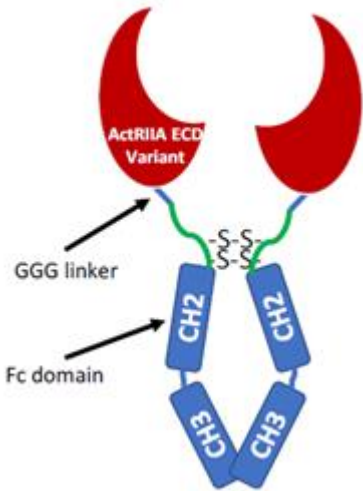
3.0 PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

3.1 Molecular Formula and Chemical Name

Elritercept is a homodimeric protein comprised of 2 disulfide-linked single chain polypeptides. Each single chain is a fusion protein consisting of a modified ECD of the human ActRIIA fused to the Fc domain of IgG1 including the hinge region, CH2, and CH3 domains by a 3-glycine amino acid linker. The elritercept molecular formula and structure are provided in [Table 3.a](#).

Table 3.a Elritercept Structure and Properties

Elritercept (TAK-226) Structure:



Laboratory Code:

KER-050
TAK-226

Table 3.a Elritercept Structure and Properties

INN/USAN:	Elritercept
Molecular Formula:	C ₁₆₉₀ H ₂₅₈₉ N ₄₅₃ O ₅₂₆ S ₂₀
Molecular Weight (Predicted Mass):	38.3 kDa for reduced single chain, 76.6 kDa for intact monomer (single chain homodimer)

3.2 Physical, Chemical, and Pharmaceutical Properties

The physicochemical properties of elritercept are provided in [Table 3.b](#).

Table 3.b Physicochemical Properties of TAK-226 Drug Substance

Parameter	Property
Theoretical isoelectric point ^a	5.5
Experimental extinction coefficient	1.60 mL·mg ⁻¹ ·cm ⁻¹

^a Theoretical value determined based upon the non-glycosylated protein sequence.

3.3 Formulation

Elritercept drug product is a solution for injection and has 2 formulations: Process II and Process III, which are described in [Table 3.c](#).

Table 3.c Elritercept Drug Product Formulations Including Excipients

Parameter	Process II	Process III ^a
Appearance	Clear to slightly opalescent solution	Clear to slightly brown to yellow and slightly opalescent
Dose Concentration per Vial	75 mg/mL	100 mg/mL
Size of Vial	2R vial	2R vial
Active Ingredient	elritercept	elritercept
Excipients	histidine NaCl polysorbate 80	histidine NaCl arginine sucrose polysorbate 80
pH	6.0 ± 0.5	6.3 ± 0.5
Mode of Administration	Subcutaneous injection	Subcutaneous injection
Storage	Refrigerated (2°C to 8°C)	Refrigerated (2°C to 8°C)

^a The Process III is an optimized formulation for the elritercept drug product, was produced to support clinical dosing at a higher dose (up to 5.0 mg/kg)

Any placebo generated for clinical use will match the drug product formulation, minus the active pharmaceutical ingredient.

For specific information about the storage and handling of elritercept drug product, refer to the Study or Pharmacy Manual associated with a given trial protocol, or the Instructions for Use contained in the shipping package.

4.0 NONCLINICAL STUDIES

4.1 Introduction

A comprehensive series of nonclinical studies was conducted to evaluate the nonclinical PD, PK, and potential toxicologic profile of elritercept and support clinical development. Key results are described in Sections 4.2 through 4.4. GLP nonclinical studies presented in this IB have been carried out in the United States (US), a member country in the OECD Mutual Acceptance of Data process, and in compliance with OECD GLP guidelines.

4.2 Nonclinical Pharmacology

RKER-050 and elritercept (formerly known as ActRIIA/B-Fc) are referred to in the nonclinical pharmacology sections of this IB. RKER-050 has an identical ECD amino acid sequence as elritercept however, the Fc domain is mouse instead of human and production cell line can differ. This reduced the overall ADA response in rodent models.

4.2.1 Pharmacodynamic Activity Related to the Proposed Mechanism of Action

4.2.1.1 *In Vitro Pharmacology Potency and Selectivity*

Two assays were used for the initial in vitro evaluation: ligand affinities (K_D) initially, followed by cellular inhibition (IC_{50}) to predict potency. Ligand affinities were measured via surface plasmon resonance (Bia core T200), and cellular inhibition was determined using luciferase reporter systems. HEK 293 cells containing a SMAD binding element SBE-Luc construct were used for all ligands except for the BMPs, which were evaluated using C2C12 cells containing a BMP-responsive BRE-Luc construct.

The affinities of elritercept for a panel of commercially available TGF- β superfamily ligands (R&D Systems) were evaluated, and the cellular inhibition of a subset of these was subsequently assessed. Based on the affinities of elritercept for the ligands, 5 ligands of interest were identified: activin A, activin B, GDF11, GDF8, and BMP9. The results for these 5 key ligands are shown in Table 4.a. Activin A, activin B, GDF11, and GDF8 are the ligands with tightest binding affinities (9 to 32 pM K_D values and 71 to 120 ng/mL IC_{50} values) and are proposed to be the primary ligands modulating the pharmacological effects of elritercept (Report KTR-02; Report KTR-03). GDF11 is an accepted surrogate for GDF8 in vitro, as they share 90% amino acid identity; therefore, the IC_{50} value for GDF11 can be extrapolated to GDF8.

Several other ligands in the TGF- β superfamily were evaluated, including other GDFs, BMPs, and TGFs; however, binding was weaker, with affinities in the high pM to nM range. Importantly, elritercept does not target BMP9, having $>30 \times$ weaker affinity and $>300 \times$ weaker cellular inhibition as compared with the target ligands. The activity of BMP9 is believed to be

critical in vascular remodeling and sparing this ligand has been proposed to be important to avoid telangiectasias and occasional epistaxis seen with a related molecule ([Ruiz et al. 2016](#)).

Table 4.a Elritercept Ligand Affinities (K_D) and Cellular Inhibition (IC_{50}) for Key TGF- β Superfamily Ligands

Ligand	K_D (pM)	IC_{50} (ng/mL)
Activin A	32	120
Activin B	19	71
GDF11	9	120
GDF8	25	Not tested
BMP9	1,000	39,000

4.2.1.2 *In Vivo Pharmacology*

Several *in vivo* pharmacology studies were performed in healthy and diseased mice to assess the pharmacology of elritercept to increase the maturation of bone marrow-derived blood cells. Nonclinical studies were conducted with elritercept or RKER-050. RKER-050 has been characterized as having similar ligand binding properties and PD effects in mice as compared with elritercept and is used in rodent nonclinical studies to avoid formation of an ADA response.

In vivo pharmacology studies in healthy wild-type mice demonstrated that elritercept induced erythropoiesis and acted, at least in part, independently of erythropoietin. In addition, elritercept increased circulating platelets (Report KT-273). Furthermore, elritercept promoted differentiation of early and late stages of erythroid precursor cells, resulting in dynamic movement of precursor cells through the different erythroid stages (Report KT-240, Report KT-273). In rodent disease models of MDS and MF, elritercept reversed anemia due to MDS or MF, as well as reversed anemia caused by ruxolitinib treatment (Report KT-239; Report KT-374; Report KT-469). In addition to improvements in hematopoiesis, elritercept improved muscle and bone mass in wild-type mice (Report KT-94, Report KT-58), reversed bone loss in MDS mice with a return to bone volume levels observed in healthy mice (Report KTX-314) and protected against muscle fibrosis in rodent disease models (Report KT-134). Taken together, commonalities in the development of fibrosis in different tissues could support a potential beneficial effect of elritercept in improving bone marrow fibrosis. Elritercept also demonstrated a reduction in pressure overload-induced cardiac hypertrophy, indicating that elritercept may also provide benefit to patients with cardiovascular disease, a common comorbidity in patients with MDS and MF (Report KT-190). A summary of relevant *in vitro* and *in vivo* pharmacology studies is presented in [Appendix B](#).

4.2.2 **Safety Pharmacology**

Two *in vivo* safety pharmacology studies were performed. One study investigated the potential impact of elritercept on retinal vascularization during development in neonatal mice as regulated by BMP9 and BMP10 and demonstrated no impact on vascular development in this *in vivo*

model. An additional in vitro study was conducted to evaluate the potential of elritercept to trigger cytokine release in unstimulated human whole blood samples derived from 10 healthy human donors. Elritercept concentrations ranging from 0.5 to 500 µg/mL (up to approximately 18-fold higher than the predicted human $C_{\max}$ were assessed. Overall, there were minimal changes in cytokine expression with elritercept, suggesting that elritercept is unlikely to trigger cytokine release in humans.

While dedicated safety pharmacology studies were not conducted, safety pharmacology assessments were included in the GLP repeat-dose toxicity studies in rats and NHPs and there were no elritercept-related effects on cardiovascular, respiratory, or central nervous system parameters. Results are described in Section 4.4 below.

4.3 Nonclinical Pharmacokinetics and Product Metabolism

To evaluate the absorption, distribution, and elimination properties of elritercept, both single- and repeat-dose PK studies were performed. The single-dose studies were carried out in rats and NHPs and were non-GLP. In NHPs, intravenous and SC administration of elritercept were assessed, and SC administration was evaluated in rats. Non-validated enzyme-linked immunosorbent assay methods were used for quantification of elritercept in the non-GLP single-dose PK studies.

Overall, these studies demonstrated that elritercept has a long $t_{1/2}$ and the exposure is generally dose-proportional.

TK and immunogenicity assessments were included in the repeat-dose GLP studies in rats for up to 3 months of either weekly (QW; 35-day) or twice weekly (BIW; 3-month) SC administration and NHPs for up to 6 months of SC administration every other week (Q2W; [Appendix A](#)). For these GLP repeat-dose toxicology studies, validated electrochemiluminescence methods were used to support the TK. Analyses of these studies determined exposure was independent of sex for both rats and NHPs.

In rats, $C_{\max}$ and AUC from time 0 (dosing) to 168 hours post-dose ($AUC_{0-168hr}$) values of elritercept increased with increasing dose in an approximately dose-proportional manner following a single dose, and in a less than dose-proportional manner following repeat administration at doses up to 50 mg/kg/dose and regimens up to BIW SC administration. The lowered dose proportionality following repeat administration is likely due to ADA production, which may have resulted in reduced exposures when compared with Day 1 values in all rat toxicity studies.

In NHPs, following SC injection of elritercept Q2W, mean $C_{\max}$, $AUC_{0-168hr}$, and/or $AUC_{0-336hr}$ values of elritercept increased with increasing dose in an approximately dose-proportional manner following single or repeat administration. Systemic exposure to elritercept appeared the same or increased slightly (<2-fold) following repeated administration of elritercept in all toxicology studies conducted in NHPs. The presence of ADA was observed following repeat administration in the 35-day (1 male at 10 mg/kg/dose) and 6-month (1 male at 3 mg/kg/dose and 1 female at 10 mg/kg/dose) toxicity studies. Although the systemic exposure did not appear to be impacted by ADA in the single animal in the 35-day study, the 2 animals in the 6-month study

were observed with lower exposures when compared with the group mean values, and therefore were considered impacted by ADA. The full analysis and results of TK parameters from rat and NHP toxicity studies are provided in [Appendix A](#).

Elritercept is a biologic therapeutic and therefore is not predicted to interfere with absorption or clearance of other drugs or expression or activity of drug metabolizing enzymes. As a consequence, no clinically relevant drug-drug interactions are expected.

4.4 Toxicology

The pivotal studies were conducted under GLP conditions at facilities that held GLP certificates or underwent GLP inspections. All nonclinical studies were conducted in North America using study designs and parameters that were consistent with accepted principles and practices as outlined in GLP: Good Laboratory Practice for Nonclinical Laboratory Studies, US Code of Federal Regulations (21 CFR Part 58), and the US is a member of the OECD Mutual Acceptance of Data Program.

A summary of the repeat-dose toxicology studies conducted to date is presented in [Table 4.b](#) and is described in detail below.

Table 4.b Good Laboratory Practice Repeat-Dose Toxicology/Pharmacokinetics Studies with Elritercept

Study Number and Title	Species/Strain	Duration of Dosing, Dose, and Frequency
2697-005 KER-050: A 35-Day Subcutaneous Toxicity Study in Rats with a 28-Day Recovery Period	Sprague Dawley rat	35 days (5 doses) 0, 3, 10, 50 mg/kg SC QW
2849-002 and 2849-002 Final Report Amendment 1 KER-050: A 3-Month Subcutaneous Toxicity Study in Rats with a 4-Week Recovery Period in Females and 10-Week Recovery in Males	Sprague Dawley rat	3 months (26 doses) 0, 3, 10, 50 mg/kg SC BIW
2697-006 KER-050: A 35-Day Subcutaneous Toxicity Study in Monkeys with a 31-Day Recovery Period	Cynomolgus monkey	35 days (3 doses) 0, 3, 10, 50 mg/kg SC Q2W
2849-001 KER-050: A 3-Month Subcutaneous Toxicity Study in Monkeys with a 2-Month Recovery Period	Cynomolgus monkey	3 months (7 doses) 0, 3, 10, 50 mg/kg SC Q2W
2849-007 KER-050: A 6-Month Subcutaneous Toxicity Study in Monkeys with a 3-Month Recovery Period	Cynomolgus monkey	6 months (13 doses) 0, 3, 10, 30 mg/kg SC Q2W
20344221 KER-050: An Enhanced	Sprague Dawley rat	Gestational Days 6 to 21 (2 doses) 0, 3, 10, 50 mg/kg SC QW

CONFIDENTIAL

Table 4.b Good Laboratory Practice Repeat-Dose Toxicology/Pharmacokinetics Studies with Elritercept

Study Number and Title	Species/Strain	Duration of Dosing, Dose, and Frequency
Preliminary Embryo-Fetal Development Study in Rats		
20344225 KER-050: A Fertility Study Administered by Subcutaneous Injection (bolus) in Male and Female Rats	Sprague Dawley rat	Males: 53 days (16 doses) Females: 15 days (before cohabitation, 5 doses) and 14 days (Gestation, 2 doses) 0, 3, 10, 50 mg/kg SC BIW

4.4.1 Repeat-Dose Studies

A series of pivotal repeat-dose GLP toxicology studies were conducted with elritercept for 35 days and 3 months duration in Sprague Dawley rats and for 35 days, 3 months, and 6 months duration in NHPs (cynomolgus monkeys). Based on elritercept's exposure profile, and the intended frequency of dosing in the clinic, repeat-dose toxicology studies were designed with intermittent SC dosing (QW or BIW in rats, Q2W in NHPs). Recovery groups were also included and ranged from 4 weeks to 3 months without administration of elritercept. Central nervous system and respiratory safety pharmacology evaluations were included in the GLP 35-day rat study and jacketed-external telemetry heart rate and ECG monitoring were included in the GLP 35-day NHP study with additional ECG monitoring in the 3- and 6-month NHP studies, with no elritercept-related findings reported. As elritercept is a high molecular weight fusion protein, TK and immunogenicity analyses were also conducted in the repeat-dose GLP studies.

Key findings in the repeat-dose toxicity studies included mortality (rat, 3-month study, high dose only) and effects on kidney (rats and NHPs), adrenal gland (rats), bone (rats), liver (rats), salivary gland (NHPs), reproductive tissues (rats and NHPs) and increases in red cell mass (rats and NHPs). Most of these key findings were observed in the high-dose groups and were reversible. Exceptions included changes in reproductive tissues that were not limited to the high-dose group and adrenal gland changes in rats, which trended toward reversibility but were not fully reversible. Only the findings from the subchronic and chronic toxicity studies are presented below.

4.4.1.1 A 3-Month Sprague Dawley Rat Study with a 4-Week Recovery Period in Females and 10-Week in Males (GLP)

In a GLP-compliant study, elritercept was administered to Sprague Dawley rats by SC injection at dose levels of 0, 3, 10, and 50 mg/kg/dose BIW for 3 months (26 total doses) followed by a 4-week (females) or 10-week (males) post-dose observation period (Report 2849-002). There were 2 early deaths in males at 50 mg/kg/dose: 1 male was euthanized because of urinary tract changes, while the cause of death for the other was undetermined. Adverse findings at 10 mg/kg/dose were observed in the kidney, adrenal glands, and femur, all of which persisted

after the recovery period. Clinical observations at ≥ 10 mg/kg/dose included impaired limb function and/or swelling. Hematology changes at ≥ 10 mg/kg/dose included increased red cell mass, neutrophils, and/or fibrinogen. At 50 mg/kg/dose there was increased ALT and AST with correlating hepatocellular vacuolation.

Additional non-adverse changes included the heart, bone marrow, femorotibial joint, ovaries, and vagina. In males only there was a elritercept-related exacerbation of a cardiomyopathy, which is a common background finding in rats ([Chanut et al. 2013](#)). Additionally, in two 50 mg/kg/dose males there was decreased epididymal weight with reduced luminal sperm and bilateral degeneration/atrophy of seminiferous tubules in the testes. These male reproductive tract changes were considered secondary to altered thermoregulation of the testes because of hindlimb weakness.

Across all 3 elritercept dose levels, the incidence of positive ADA results on Day 92 was 44% (16 of 36 animals). The presence of ADA to elritercept appeared to impact systemic exposure with the greatest impact observed at the 3 and 10 mg/kg/dose groups.

Based on these findings, the NOAEL of elritercept in Sprague Dawley rats was 3 mg/kg/dose, the lowest dose tested. This dose corresponded to a sex-combined mean Day 85 C_{max} and $AUC_{0-168hr}$ values of 5.88 $\mu\text{g/mL}$ and 765 $\text{hr} \cdot \mu\text{g/mL}$, respectively. Because of ADA response to the molecule, peak exposure levels at this dose occurred on Day 1 and corresponded with C_{max} and $AUC_{0-168hr}$ values of 41.8 $\mu\text{g/mL}$ and 4,570 $\text{hr} \cdot \mu\text{g/mL}$, respectively.

4.4.1.2 A 3-Month Subcutaneous Toxicity Study in NHPs with a 8-Week Recovery Period (GLP)

A GLP-compliant study was conducted to assess the potential toxicity and TK profile of elritercept in NHPs (cynomolgus monkeys) when administered by SC injection for 3 months (Report 2849-001). Administration of elritercept via SC injection to NHPs at dose levels of 0, 3, 10, and 50 mg/kg/dose Q2W for 13 weeks (7 total doses) followed by an 8-week recovery period was tolerated at all dose levels. At 50 mg/kg/dose there were partially reversible adverse effects in the kidney (hemorrhage and fibrosis) along with corresponding non-adverse increased kidney weight, edema, and corresponding serum chemistry changes.

At all dose levels there was non-adverse dose-dependent increased hematopoietic cellularity in the bone marrow that demonstrated evidence of reversibility and correlated with hematology changes that included increased RBC mass parameters, erythrocyte indices, and reticulocytes. Additional changes at ≥ 10 mg/kg/dose included effects on the kidney, mammary, and salivary glands, and at 50 mg/kg/dose reversible increased liver (with gallbladder) weight, and changes in serum chemistry indicative of an inflammatory response.

All animals (6/sex/dose group) were negative for ADA on Day 85. Systemic exposure to elritercept was independent of sex and did not appear to change following repeated administration.

Based on these findings, the NOAEL of elritercept was 10 mg/kg/dose. This dose corresponded to sex combined mean Day 85 C_{max} , $AUC_{0-168hr}$, and $AUC_{0-336hr}$ values of 147 $\mu\text{g/mL}$, 19,500 $\text{hr} \cdot \mu\text{g/mL}$, and 28,000 $\text{hr} \cdot \mu\text{g/mL}$, respectively.

4.4.1.3 A 6-Month Subcutaneous Toxicity Study in NHPs with a 3-Month Recovery Period (GLP)

In a GLP-compliant study, elritercept was administered to NHPs (cynomolgus monkeys) via SC injection at dose levels of 0, 3, 10, and 30 mg/kg/dose Q2W (up to 13 total doses) for 26 weeks followed by a 12-week post-dose recovery period and was tolerated at all dose levels (Report 2849-007). There were 3 unscheduled death of animals, including 1 male during the pre-study acclimation period, and two (1 male at 3 mg/kg/dose and 1 male at 30 mg/kg/dose) during the dosing phase of the study; the causes of moribund conditions and/or morbidity was due to cachexia/stress. These early deaths were not considered elritercept-related because there were no similar findings in animals that received higher doses of elritercept for longer durations.

At all dose levels, there was a non-adverse dose-related increased RBC mass parameters (erythrocyte count, Hgb concentration, and HCT), with concurrent increased absolute reticulocyte counts in males at ≥ 10 mg/kg/dose and females at ≥ 3 mg/kg/dose. At ≥ 10 mg/kg/dose, there were changes in erythrocyte indices that were indicative of production of smaller erythrocytes. Hematology changes were reversible with the exception of persistent increased RBC distribution width at 30 mg/kg/dose.

Kidney changes at ≥ 10 mg/kg/dose included edema, hemorrhage, interstitial pigment consistent with hemosiderin, and/or fibrosis with correlative changes in serum markers (increased urea nitrogen, creatinine, and potassium with decreased chloride). All of these findings were non-adverse and were reversible or partially reversible.

Lastly, at the 30 mg/kg/dose, there was a reversible increase in AST and ALT activities and increased triglycerides, none of which had a microscopic correlate.

All animals (6/sex/dose/group) were negative for ADA on Days 1, 169, and 266, with the exception of 1 male at 3 mg/kg/dose on Day 169 and 1 female at 10 mg/kg/dose on Days 169 and 266. The positive ADA responses appeared to impact the serum concentration-time profile for these animals on Day 169. As a group, systemic exposure to elritercept was independent of sex and did not appear to change following repeated administration.

Based on these findings, the NOAEL of elritercept was 30 mg/kg/dose. This dose corresponded to mean (sex combined) Day 169 C_{max} , $AUC_{0-168hr}$, and AUC calculated from time 0 (dosing) to the last quantifiable concentration (AUC_{last}) values of 315 $\mu\text{g/mL}$, 37,000 $\text{hr} \cdot \mu\text{g/mL}$, and 48,600 $\text{hr} \cdot \mu\text{g/mL}$, respectively.

4.4.2 Genotoxicity (Mutagenicity)

Elritercept is a biotherapeutic; therefore, per ICH Guideline S6-R1: *Biotechnology Products* {ICH, 2011 #90}, no genotoxicity studies have been completed.

4.4.3 Carcinogenicity

Elritercept is a biotherapeutic; therefore, per International Council for Harmonisation (ICH) Guideline S6-R1: *Biotechnology Products*, no carcinogenicity studies have been completed.

4.4.4 Reproductive Toxicity

A preliminary enhanced embryo-fetal development toxicity study indicated the potential for embryo-fetal toxicity (Report 20344221). Elritercept is anticipated to reduce reproductive function as a result of its on-target inhibition of activin ([Wijayarathna and de Kretser 2016](#)). This is consistent with the findings in the repeat-dose toxicity studies where reproductive tissues (mammary glands, ovaries, vagina) were affected. There were no effects on fertility in either males or females in a rat fertility study, however, in females there was persistent diestrus that prolonged the estrus cycle (Report 20344225). Details for both reproductive toxicity studies are provided below.

4.4.4.1 An Enhanced Preliminary Embryo-Fetal Development Study in Rats

A GLP-compliant study was conducted to provide a preliminary evaluation of elritercept on pregnant Sprague Dawley rats and the development of the embryo and fetus. Administration of elritercept by QW SC injection on GD 6 and GD13 was tolerated in pregnant rats at dose levels of 0, 3, 10, and 50 mg/kg/dose (Report 20344221). Based on these results, the maternal NOAEL was 50 mg/kg/dose, the highest dose tested, and corresponded to a $C_{\max}$ of 151 $\mu\text{g/mL}$ and an AUC_{last} of 10,100 $\text{hr} \cdot \mu\text{g/mL}$ on GD13. Maternal administration of elritercept reduced embryo-fetal viability at 10 and 50 mg/kg/dose and reduced fetal body weights at 50 mg/kg/dose. There were no elritercept-related malformations or variations at fetal external, visceral, or skeletal examination.

Based on the available data and the number of litters evaluated, the developmental NOAEL for elritercept was 3 mg/kg/dose (lowest dose tested), which corresponds to a maternal $C_{\max}$ of 27.8 $\mu\text{g/mL}$ and maternal AUC_{last} of 2,030 $\text{hr} \cdot \mu\text{g/mL}$ on GD13.

4.4.4.2 A Fertility Study Administered by Subcutaneous Injection (Bolus) in Male and Female Rats

In a GLP-compliant study to evaluate fertility of male and female Sprague Dawley rats, elritercept was administered by SC injection to rats twice weekly (BIW) at dose levels of 0, 3, 10, or 50 mg/kg/dose (Report 20344225). A total of 88 male and 88 female rats were randomly assigned to 4 dose groups (Groups 1 through 4), with 22 rats/sex/group. The male rats were administered via SC injection (bolus) the test article, elritercept, or the vehicle control article, BIW, starting 28 days before cohabitation, during cohabitation, and continuing through the day before euthanasia for a minimum of 53 days (16 total doses). The female rats were administered elritercept, or the vehicle control article, BIW, by the same route starting 15 days before cohabitation, during cohabitation, and continuing until GD7 (≥ 7 total doses).

Males

There were no elritercept-related effects on male mating or fertility parameters at any dose level. There were no elritercept-related effects on sperm parameters as assessed by percent sperm motility and sperm density. There were elritercept-related effects on sperm morphology (increased detached heads and broken tails) at 50 mg/kg/dose, but these increases were not considered adverse because they did not have any effect on the fertility of the males and the mean values of detached head were within the historical control range (1.6 to 11.5) of the testing facility. The mean value of sperm with broken tail at 50 mg/kg/dose (1.3) was comparable to the concurrent vehicle controls (1.5). Therefore, elritercept-related effects on sperm morphology at 50 mg/kg/dose were not considered adverse.

Females

There were no elritercept-related effects on the mating, fertility, or pregnancy indices at any dose level. The mating index was 95.5%, 100.0%, and 100.0% at 3, 10, and 50 mg/kg/dose, respectively, compared with 100.0% in vehicle controls. The fertility index was 90.5%, 95.5%, and 100% in the 3, 10, and 50 mg/kg/dose groups, respectively, compared with 95.5% in vehicle controls. The pregnancy index was 86.4%, 95.5%, and 100.0% at 3, 10, and 50 mg/kg/dose, respectively, compared with 95.5% in vehicle controls. There were no elritercept-related effects on any ovarian or uterine parameter at any dose level, including number of corpora lutea, implantation sites, and live or dead embryos. There was an elritercept-related increase in ovarian weights at 50 mg/kg/dose that was attributed to variation in the number of corpora lutea present but was not considered adverse as there were no impacts on fertility endpoints measured in this study.

Overall, there were no sex differences observed on Days 1 and 15 in systemic exposure of elritercept. Mean peak (C_{max}) and total (AUC_{last}) exposure values increased in a generally less-than-dose-proportional manner across the dose range on Days 1 and 15. Accumulation ratios on Day 15 ranged from 0.147 to 0.365, with a high number of ADA-positive animals suggesting that exposure may have been reduced by ADAs.

In conclusion, male and female Crl:CD(SD) rats were administered elritercept via SC injection (bolus) BIW before cohabitation (28 and 15 days prior to mating for males and females, respectively), during cohabitation, and through the day prior to necropsy for males and GD7 for females at dose levels of 0, 3, 10, and 50 mg/kg/dose. In the males, no elritercept toxicological effects were observed in mean body weight, body weight gain, and food consumption. Non-adverse elritercept-related effects on sperm morphology were observed at 50 mg/kg/dose. In pre-mating females, elritercept administration resulted in increases in mean body weight at ≥ 10 mg/kg/dose and in mean body weight gain at ≥ 3 mg/kg/dose. In gestating females, there were elritercept-related increases in mean maternal body weight at 50 mg/kg/dose. Therefore, because none of the changes observed were adverse, the NOAEL for general toxicity was 50 mg/kg/dose for both sexes.

There were no effects on fertility in either males or females. In males, elritercept at 50 mg/kg/dose resulted in non-adverse changes in sperm morphology. In females, elritercept caused persistent diestrus, which prolonged the length of the estrous cycle of females treated at ≥ 10 mg/kg/dose, as well as an increase in ovarian weights at 50 mg/kg/dose; however, these did

not affect female fertility and there were no effects on the mating, fertility, or pregnancy incidences. There were also no elritercept-related effects on ovarian or uterine parameters at any dose level. Therefore, the reproductive NOAEL was 50 mg/kg/dose, which in males corresponded to a Day 15 $C_{\max}$ of 51.5 $\mu\text{g/mL}$ and $\text{AUC}_{0-168\text{hr}}$ of 2,900 $\text{hr}\cdot\mu\text{g/mL}$, and in females corresponded to a Day 15 $C_{\max}$ of 48.5 $\mu\text{g/mL}$ and $\text{AUC}_{0-168\text{hr}}$ of 2,270 $\text{hr}\cdot\mu\text{g/mL}$.

4.4.5 Other Toxicity Studies

4.4.5.1 Local Tolerance

Stand-alone nonclinical studies were not conducted to evaluate local tolerability. However, evaluation of injection sites was performed in all repeat-dose toxicity studies in rats and monkeys by the SC route of administration.

Elritercept was well tolerated locally following SC administration. Dose administration sites were routinely monitored throughout the dosing period and the tissues were collected at necropsy and assessed for both macro- and microscopic findings. No clinical observations or macro- or microscopic findings were observed for any of the studies conducted in rats or NHPs.

5.0 EFFECTS IN HUMANS

5.1 Overview of the Elritercept Clinical Program

The clinical program of elritercept includes 4 clinical trials initiated by Keros and 1 clinical trial initiated by Hansoh.

Under the terms of Takeda's Exclusive License Agreement with Keros Therapeutics, Inc. to develop, commercialize, and manufacture elritercept outside of mainland China, Hong Kong, and Macau, Takeda is developing elritercept (known as TAK-226; KER-050) for the potential treatment of anemia in adults with very low-, low-, or intermediate-risk (lower-risk; [LR]) MDS; more recently defined as myelodysplastic neoplasms) and for the potential treatment of anemia associated with MF in adults.

As of 03 April 2025, overall, 262 participants have been enrolled in the elritercept clinical development program (Keros-initiated and Hansoh-initiated trials), of which 252 participants received elritercept (241 in 3 Keros-initiated trials and 11 in 1 Hansoh-initiated trial).

The 4 Keros-initiated clinical trials include: a phase 1 dose-escalation trial in healthy postmenopausal women (Study KER-050-01); a phase 2 open-label, ascending-dose trial in participants with MDS (Study KER050-MD-201); and a phase 2 open-label, ascending-dose trial in participants with MF (Study KER050-MF-301). In addition, a phase 3 double-blind, placebo-controlled trial in participants with LR-MDS (KER-050-D301) is currently ongoing and a phase 3 trial of elritercept versus ESA for the treatment of transfusion-dependent anemia in ESA-naïve adult participants with LR-MDS is planned. An overview of the completed or ongoing elritercept Keros-initiated clinical trials is provided in [Table 5.a](#).

Hansoh, a licensing partner with Keros, which holds development rights for elritercept in the territory of mainland China, Hong Kong, and Macau, has initiated a phase 2 clinical trial of

elritercept in adults with anemia due to LR-MDS in China. The trial ("Study HS-2016-201"), which is entitled "A Phase II Study Evaluating Efficacy, Safety, and Pharmacokinetics of HS-20106 in IPSS-R Very Low/Low/Intermediate-Risk MDS Patients with Anemia" has enrolled 11 participants to date.

Table 5.a Overview of Completed and Ongoing Keros-Initiated Elritercept Clinical Studies (as of 03 April 2025)

Study Number (Phase)	No. of Participants	Population	Study Design	Primary Objective	Status
KER-050-01 (phase 1)	SAD: 38 (elritercept 30; placebo 8) MAD: 10 (elritercept 8, placebo 2)	Healthy postmenopausal women aged 45 to 75 years old	Randomized, double-blind, placebo-controlled, single ascending and multiple-dose administration 2-part trial in healthy postmenopausal women	Safety, tolerability, pharmacokinetics of escalating doses of elritercept administered as single and multiple SC doses	Completed
KER050-MD-201 (phase 2)	Planned enrollment: Approximately 140 Enrollment ongoing, enrolled as of DCO date: 109	Males or females aged ≥18 years old	Open-label, ascending-dose, 2-part trial to evaluate the effects of elritercept on anemia in participants with very low-, low-, or intermediate-risk MDS who are not currently receiving treatment with an ESA	Part 1 Dose Escalation: Safety and tolerability of ascending doses of elritercept to determine the dose(s) that will be evaluated in Part 2 of the trial Part 2 Dose Confirmation: Confirm safety and tolerability of the dose(s) selected in Part 1 LTE: Long-term safety and tolerability of elritercept	Ongoing

Table 5.a Overview of Completed and Ongoing Keros-Initiated Elritercept Clinical Studies (as of 03 April 2025)

Study Number (Phase)	No. of Participants	Population	Study Design	Primary Objective	Status
KER050-MF-301 (phase 2)	Planned enrollment: Approximately 120 Enrollment ongoing, enrolled as of DCO: 94 monotherapy: 36 Combination therapy: 58	Males or females aged ≥18 years old	Open-label, multiple ascending-dose trial to evaluate the safety, tolerability, PK, PD, and efficacy of elritercept administered with or without ruxolitinib, in participants with PMF, post-ET MF, or post-PV MF	Part 1 Dose Escalation: Safety and tolerability of ascending doses of elritercept monotherapy and in combination with ruxolitinib to determine the RP2D(s) for Part 2 Part 2 Dose Expansion: Safety and tolerability of the dose(s) selected in Part 1 LTE: Long-term safety and tolerability of elritercept administered with or without ruxolitinib	Ongoing
KER-050-D301 (phase 3)	Planned enrollment: Approximately 225 Enrollment ongoing; no participants enrolled	Males or females aged ≥18 years	Randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of elritercept for the treatment of anemia in adult participants with transfusion-dependent very low-, low-, or intermediate-risk MDS	To evaluate the efficacy of elritercept in reducing RBC transfusions	Ongoing

Source: Table 14.1.1.LT; Table 14.1.1.1

Data presented above are as of the date of the final clinical study report of 10 September 2021 for Study KER-050-01 and the DCO date of 03 April 2025 for Study KER050-MD-201, Study KER050-MF-301 and Study KER-050-D301

5.1.1 Study Subjects

5.1.1.1 Study KER-050-01: Completed – Phase 1, First-in-Human

Study KER-050-01 was a phase 1, FIH, randomized, double-blind, placebo-controlled, 2-part, dose-escalation trial to evaluate the safety, tolerability, PK, and PD effects of elritercept. This trial was conducted in 48 healthy postmenopausal women, 38 of whom received ≥ 1 dose of elritercept and 10 of whom received placebo. This trial evaluated the safety and tolerability of elritercept over the dose range 0.05 to 4.5 mg/kg administered as a single dose in Part 1 (single ascending dose [SAD]) and 2 doses of 0.75 mg/kg elritercept in Part 2 (multiple ascending dose [MAD]) administered 28 days apart.

Safety results are provided Section in [5.3.1](#), PK results are provided in Section [5.2.1.1](#) and PD results are provided in Section [5.2.2.1](#) as of the clinical study report finalization date of 10 September 2021.

5.1.1.2 Study KER050-MD-201: Ongoing – Phase 2

Study KER050-MD-201 is an ongoing phase 2, open-label, 2-part ascending-dose trial to evaluate the safety and tolerability of elritercept and the effects of elritercept on anemia in participants with LR-MDS, with or without RS, or CMML who are not currently receiving treatment with an ESA. This 2-part trial includes dose escalation in Part 1 followed by dose confirmation in Part 2.

Part 1 (Dose Escalation) was designed to evaluate and identify the elritercept dose(s) to be evaluated in Part 2. Dose escalation began at 0.75 mg/kg every 28 days, with 5 dose levels and approximately 6 participants per dosing cohort (N=31 participants total for Part 1).

Approximately equal numbers of RS-positive and non-RS participants with LR-MDS were enrolled in each dosing cohort (that is, 3 RS-positive + 3 non-RS). Participants in Part 1 received SC administered elritercept every 28 days for up to 24 cycles.

In this trial, Part 1 Dose Escalation is further divided into 2 phases. The first phase evaluates Cycles 1 through 4 of treatment for each of the 5 dosing cohorts (0.75 to 5.0 mg/kg). For the purpose of the IB, the first phase will hereafter be called the “Base Study.” The second phase follows participants from Cycles 5 through 24, which will hereafter be referred to as the “Part 1 Extension Period”. Dosing in the Part 1 Extension Period is based on the highest dose cleared by the Safety Review Committee (SRC) at the time of entry into the Part 1 Extension Period, and participants not already on the RP2D of 3.75 mg/kg and 5.0 mg/kg titrated up to this dose once the RP2D was identified. In Part 2 (Dose Confirmation), all participants-initiated treatment at the starting dose of 3.75 mg/kg and received up to 24 cycles of treatment.

The primary objective of Part 2 is to confirm the safety and tolerability of the dose(s) selected in Part 1. Participants will be enrolled into 1 of 6 cohorts according to their LR-MDS or CMML diagnosis, RS and/or iron overload status, and RBC transfusion requirements during the Pretreatment Period:

- Cohort A: Participants with RS-positive LR-MDS requiring RBC transfusions
- Cohort B: Participants with non-RS LR-MDS requiring RBC transfusions
- Cohort C: NT participants with either RS-positive LR-MDS or non-RS LR-MDS
- Cohort D: Participants with CMML and anemia
- Cohort E: Participants with LR-MDS (either RS-positive or non-RS) requiring RBC transfusions, with iron overload, who are receiving iron chelation therapy
- Cohort F: Participants with LR-MDS (either RS-positive or non-RS) requiring RBC transfusions, with iron overload, who are not receiving iron chelation therapy

Approximately 110 participants will be enrolled in Part 2 and will receive SC-administered elritercept every 28 days for up to 24 dosing cycles.

Participants from Part 1 or Part 2 who complete the 24-cycle Treatment Period and may have potential benefit from continued elritercept treatment, in the opinion of the Investigator, may be eligible to enroll in the open-label Long-Term Extension (LTE). The LTE will continue until regulatory action occurs or until elritercept is no longer being developed for the treatment of MDS.

A total of 9 Part 1 participants experienced a substantial gap (>60 days) between their last dose in the Part 1 Base Study and first dose in the Part 1 Extension Period because of administrative reasons. These participants were considered to have reinitiated treatment so that the start of the Part 1 Extension Period represented their new baseline and treatment start (C1D1).

To evaluate long-term effects of elritercept treatment in LR-MDS, participants from Part 1 and Part 2 are pooled into a LTS analysis set. The LTS analysis set comprises:

- Part 1: the entire study period for the Part 1 participants with consecutive treatment in the Base Study and the Part 1 Extension Period, or the Part 1 Extension Period only (following rebaseline) for participants with a treatment gap >60 days between the Base Study and Part 1 Extension Period.
- Part 2: the entire study period.

Analyses were performed separately for the Base Study and LTS. For Part 1 participants with consecutive treatment (that is, who did not rebaseline in the Part 1 Extension Period), data from the Base Study and from Cycles 1 through 4 of the LTS are duplicated in the 2 data presentations. The LTS analysis is the focus of this IB.

Safety results are provided in Section 5.3.2, PK results are provided in Section 5.2.1.2, and PD results are provided in Section 5.2.2.2. This IB includes data available as of the DCO date of 03 April 2025 (unless otherwise stated).

5.1.1.3 Study HS-20106-201: Ongoing – Phase 2

Hansoh, a licensing partner with Keros for elritercept solely in the territory of mainland China, Hong Kong, and Macau, has initiated a phase 2 clinical trial of elritercept in adults with anemia due to LR-MDS in the territory of mainland China.

Study HS-20106-201 is a phase 2, two-part trial evaluating safety, PK, and efficacy of HS-20106 in adult participants with very low/low/intermediate-risk MDS with anemia in the territory of mainland China.

This trial consists of two parts: Part A (open-label) and Part B (randomized). The planned enrollment for the trial is 96-176 participants. Participants in all cohorts will receive SC administration of HS-20106 or placebo once every 4 weeks on day 1 of each treatment cycle. The core treatment period consists of 6 treatment cycles. The initial dose is 3.75 mg/kg and can be titrated up to 5.0 mg/kg.

5.1.1.4 Study KER050-MF-301: Ongoing – Phase 2

Study KER050-MF-301 is a phase 2, open-label, multiple ascending-dose trial to evaluate the safety, tolerability, PK, PD, and efficacy of elritercept, administered with or without ruxolitinib, in participants with PMF, post-ET MF, and post-PV MF who have anemia. This 2-part trial includes dose escalation in Part 1 followed by dose expansion in Part 2. Both Part 1 and Part 2 are designed to assess 2 different MF subpopulations in parallel arms:

- Arm A (monotherapy): elritercept monotherapy in participants with anemia who have discontinued JAK inhibitor(s) because of relapsed/refractory disease or intolerance to JAK inhibitor(s) or who are ineligible for JAK inhibitor(s).
- Arm B (combination therapy): elritercept in combination with ruxolitinib in participants with anemia who have been receiving ruxolitinib for ≥ 8 weeks prior to C1D1 and are on a stable dose of ruxolitinib for ≥ 4 weeks prior to C1D1.

In addition, Arm 2C (front-line monotherapy, in Brazil only) will evaluate elritercept monotherapy in participants with anemia who have received no prior treatment with JAK inhibitor(s) and have no access to JAK inhibitor therapy as determined by the investigator.

Part 1 (Dose Escalation) was designed to evaluate the safety and tolerability of ascending doses of elritercept monotherapy (Arm 1A) and elritercept in combination with ruxolitinib (Arm 1B) and identify the RP2D of elritercept as monotherapy and in combination with ruxolitinib in participants with MF. Both the monotherapy and combination therapy arms include 4 dosing cohorts with starting dose of 0.75 mg/kg every 28 days with approximately 6 participants per dosing cohort (N=up to 30 total participants in each arm). All participants in Part 1 will receive SC-administered elritercept on Day 1 of each 28-day dosing cycle for up to 13 cycles (52 weeks).

Part 2 (Dose Expansion) will further evaluate the safety and tolerability of the dose(s) selected in Part 1 and assess potential of elritercept to elicit anemia responses and to improve spleen size and constitutional symptoms when administered as monotherapy or in combination with

ruxolitinib. All participants in Part 2 will receive SC-administered elritercept on Day 1 of each 28-day dosing cycle for up to 13 cycles (52 weeks).

At the end of the 13-cycle (52 weeks) Treatment Period, participants who may have potential benefit from continued elritercept treatment either as monotherapy or in combination with ruxolitinib, in the opinion of the Investigator, may continue in the LTE. The LTE will continue until regulatory action occurs or until elritercept is no longer being developed for the treatment of MF.

Enrollment in Part 1 has completed and the RP2D has been identified as 3.75 mg/kg with the option to up-titrate to 5.0 mg/kg for response or down-titrate for tolerability. The RP2D was selected to align with the ongoing trial in LR-MDS and was based on SRC review of data from all 4 dose cohorts in both treatment arms.

Safety results are provided in Section 5.3.4, PK results are provided in Section 5.2.1.3, and PD results are provided in Section 5.2.2.3. All data are available as of the DCO date of 03 April 2025 (unless otherwise stated).

5.2 Clinical Pharmacology

To date, the PK and PD of elritercept have been evaluated in 3 clinical studies, Study KER-050-01 has been completed in healthy participants, Study KER050-MD-201 is currently ongoing in participants with MDS, and Study KER050-MF-301 is currently ongoing in participants with MF. All data for the ongoing studies are preliminary.

5.2.1 Pharmacokinetics

5.2.1.1 *Pharmacokinetics in Healthy Volunteers: Study KER-050-01*

Study KER-050-01 has been completed in healthy participants. This trial included 2 parts: Part 1 (SAD) consisted of 4 dose groups receiving a single elritercept dose (0.05, 0.5, 1.5, and 4.5 mg/kg) with placebo controls (n=38; 30 active and 8 placebo) and Part 2 (MAD) consisted of 1 dose group receiving 2 doses of elritercept at 0.75 mg/kg with placebo controls (n=10; 8 active and 2 placebo), administered 28 days apart.

Overall, in the SAD portion of the trial, serum elritercept concentrations increased with increasing dose, with measurable concentrations observed up to 62 days postdose following a single dose of 4.5 mg/kg.

Table 5.b summarizes elritercept PK parameters following SADs of elritercept in Part 1. Elritercept was absorbed with median T_{max} ranging from approximately 4.5 to 6 days postdose. Mean systemic exposure increased with increasing dose levels 0.5 to 4.5 mg/kg. Dose-proportionality analysis indicated an approximately proportional increase in systemic exposure. Serum elritercept $t_{1/2}$ values ranged from 11.7 to 11.9 days.

Table 5.b Summary of Key Serum Elritercept PK Parameters by Treatment – Part 1 (SAD) (PK Population; Study KER-050-01)

Elritercept Dose	Median (Range) T _{max} (hr)	Mean (CV%) C _{max} (µg/mL)	AUC _{last} (hr*µg/mL)	AUC _{0-inf} (hr*µg/mL)	t _½ (hr)	CL/F (mL/hr/kg)
0.05 mg/kg ^a (n=1)	79.0 (NA)	1.873 (NA)	340 (NA)	NA	NA	NA
0.5 mg/kg (n=8)	142.4 (68-235)	4.2336 (34%)	1,411.2 (34%)	2,172.1 ^b (19%)	282.8 ^b (45%)	0.2380 ^b (20%)
1.5 mg/kg (n=8)	108.5 (72-147)	11.7685 (36%)	5,080.6 (35%)	5,938.7 ^b (37%)	285.9 ^b (38%)	0.2864 ^b (38%)
4.5 mg/kg (n=6)	143.8 (76-239)	27.0230 (21%)	16,070.4 (24%)	17,184.8 (22%)	281.2 (15%)	0.2741 (24%)

Source: KER-050-01 CSR; Table 23

AUC_{last}: area under the serum concentration vs time curve calculated using the linear trapezoidal rule from time zero to the last observed concentration above the lower limit of quantification.

^a n=1; serum concentrations were BLQ for 7 of the 8 participants.

^b n=7; terminal phase could not be estimated for one participant.

The observed plasma PK parameters for participants receiving multiple doses of elritercept in Part 2 are summarized in [Table 5.c](#).

The serum elritercept PK of the 0.75 mg/kg multiple-dose group (Part 2) on Day 1 was generally consistent with that observed in the single dosing arm (Part 1) of the trial. Comparison of Day 29 exposure with Day 1 exposure showed minor accumulation after the second dose with a mean C_{max} ratio of 1.080 and mean Day 29 AUC_{tau} (AUC across the dosing interval, calculating using the linear trapezoidal rule) / Day 1 AUC_{last} ratio of 1.138.

Table 5.c Summary of Day 1 and Day 29 Serum Elritercept PK Parameters by Treatment – Part 2 (MAD) (PK Population; Study KER-050-01)

Elritercept Dose: 0.75 mg/kg	Median (Range) T _{max} (hr)	Mean (CV%) C _{max} (µg/mL)	AUC _{last} (hr*µg/mL)	t _½ (hr)	CL/F (mL/hr/kg)	C _{min} (µg/mL)	AUC _{tau} (hr*µg/mL)
Day 1 (n= 8)	74.2 (73-237)	4.3265 (22%)	1,574.7 (40%)	234.4 ^a (28%)	0.3188 ^a (29%)	NA	NA
Day 29 (n=8)	108.5 (72-317)	4.6554 (26%)	1,933.6 (55%)	293.3 ^b (NA)	NA	0.4624 (138%)	2620.0 ^c (10%)

Source: KER-050-01 CSR Tables 24 and 25

AUC_{last}: area under the serum concentration vs time curve calculated using the linear trapezoidal rule from time zero to the last observed concentration above the lower limit of quantification; AUC_{tau}: area under the serum concentration-time curve across the dosing interval, calculating using the linear trapezoidal rule.

Table 5.c Summary of Day 1 and Day 29 Serum Elritercept PK Parameters by Treatment – Part 2 (MAD) (PK Population; Study KER-050-01)

Elritercept Dose: 0.75 mg/kg	Median (Range) T _{max} (hr)	Mean (CV%) C _{max} (µg/mL)	AUC _{last} (hr*µg/mL)	t _½ (hr)	CL/F (mL/hr/kg)	C _{min} (µg/mL)	AUC _{tau} (hr*µg/mL)
---------------------------------	---	--	--------------------------------	---------------------	-----------------	--------------------------	-------------------------------

^a n=5.

^b n=1.

^c n=4.

Mean accumulation ratio for C_{max} (Day 29 C_{max} / Day 1 C_{max}) and AUC (Day 29 AUC_{tau} / Day 1 AUC_{last}) was approximately 1:1.

5.2.1.2 Pharmacokinetics in Participants with MDS: Study KER050-MD-201

Serum elritercept concentrations were collected during both Part 1 (Dose Escalation) and Part 2 (Dose Confirmation; RP2D) of the trial. Preliminary sparse concentration data were available from a total of 71 participants as of the 01 June 2023 DCO date used for this analysis over a dose range of 0.75 mg/kg to 5.0 mg/kg.

A preliminary popPK model was developed to characterize the PK of elritercept in participants with MDS. Weight and ADA were detected as statistically significant covariates on CL/F. A dose effect was shown on elritercept CL/F for doses higher than 3.75 mg/kg. CL/F increased with increasing body weight: compared to a typical participant with a body weight of 70 kg, a participant with body weight of 50.6 kg had a 25% lower CL/F, whereas a participant with a body weight of 157 kg had a 107% higher CL/F. The analysis supports the weight-based dosing of elritercept. Presence of ADA increased CL/F by 21% compared to participants with no ADA. The dose effect decreased CL/F by 10% in participants receiving doses higher than 3.75 mg/kg. In the context of elritercept between-subject PK variability, the dose effect is not considered clinically meaningful. Exposure to elritercept was not significantly altered by other covariates, such as sex, race, mild-to-moderate hepatic impairment, mild-to-moderate renal impairment, baseline serum EPO, baseline transfusion burden, RS status, location of SC injection, and concurrent iron chelation therapy.

The exposure-efficacy analysis evaluated effect of exposure on overall erythroid response (HI-E or TI ≥8 weeks), HI-E, and TI ≥8 weeks. Both elritercept AUC and C_{trough} showed a trend of association with the 3 efficacy endpoints, that is, overall erythroid, HI-E and TI 8-week.

5.2.1.3 Pharmacokinetics in Participants with MF: Study KER050-MF-301

Preliminary population PK/PD analyses were conducted using data from the ongoing KER050-MF-301 as of the DCO date of 03 April 2024. Elritercept C_{trough} was positively correlated with mean change in PD markers, ie, Hb, reticulocytes, and sTfR over a 12-week period post-treatment. Higher C_{trough} also showed a correlation with higher probability of meeting parameters of anemia response. This preliminary analysis shows no evidence of PK differences

between the MF and MDS populations and no substantial difference in the exposure-response, where response relates to a common endpoint for both studies: change in Hb.

5.2.1.4 *Effects on QTc*

In healthy participants (KER-050-01), QTc-concentration analysis showed that elritercept, administered either as a single dose of 0.05, 0.5, 1.5, or 4.5 mg/kg or multiple doses of 0.75 mg/kg, did not prolong QTc. There were no categorical findings of concern regarding ECG intervals or waveform abnormalities, and the data suggested no clinical concerns regarding QTc prolongation for elritercept at the doses evaluated. Similarly, in the patients with MDS (KER050-MD-201), the administration of elritercept at doses of 0.75 to 5.0 mg/kg Q4W demonstrated no relationship between elritercept concentrations and changes in heart rate and corresponding QTcF intervals (Δ QTcF). The Fridericia correction method was used in both studies to generate Δ QTc and $\Delta\Delta$ QTc in healthy participants (KER-050-01) and Δ QTc in patients with MDS (KER050-MD-201). Analysis of the QTcF versus concentrations using linear mixed-effects modeling as recommended by Garnett and colleagues, found that increasing concentrations of elritercept did not lead to increases in $\Delta\Delta$ QTc or Δ QTc in either healthy participants (KER-050-01) or patients with MDS (KER050-MD-201), respectively (FDA. (2022). Guidance for Industry: E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential — Questions and Answers. US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); Garnett et al., 2018). Therefore, elritercept is not likely to cause QTc prolongation in either the healthy participant or patients with MDS within the dose studied up to 5.0 mg/kg Q4W, which is consistent with the fact elritercept is a biological therapeutic protein with a molecular weight >70 kDa.

5.2.1.5 *Pharmacokinetic Conclusions*

Following SC administration, elritercept is absorbed with a median $T_{\max}$ of approximately 4.5 to 6 days in healthy postmenopausal women and eliminated with a mean $t_{1/2}$ of approximately 12 days. Serum elritercept exposure was dose-proportional in healthy postmenopausal women across a dose range of 0.5 to 4.5 mg/kg. No substantial evidence of accumulation has been observed in participants with LR-MDS, or MF to date. Systemic exposure increased with increasing dose in participants with LR-MDS. Preliminary popPK analyses suggested that weight has clinically meaningful effect on elritercept CL/F, supporting the weight-based dosing of elritercept. The marginal increase in exposure (<10%) by dose level was within the variability of elritercept exposures. The incidence of ADA in participants with LR-MDS and MF is low and overall does not appear to have any meaningful effects on serum elritercept exposure. Exposure to elritercept was not significantly altered by sex, race, mild-to-moderate hepatic impairment, mild-to-moderate renal impairment, baseline serum EPO, baseline transfusion burden, RS status, location of SC injection, and concurrent iron chelation therapy.

Preliminary popPK analysis showed no evidence of PK differences between the MF and LR-MDS studies, and there was no evidence that the exposure-response was different, where response related to the change in Hgb, a common endpoint for both studies. Thus, the PK/PD

analysis supports the same phase 2 dosing strategy as that utilized in LR-MDS, that is, a starting dose of 3.75 mg/kg SC Q4W, with the option to titrate up to 5.0 mg/kg or titrate down to 2.5 mg/kg based on individual response or safety findings, respectively, as well as the proposed dosing strategy in the phase 3 Study KER-050-D301.

5.2.2 Pharmacodynamics

5.2.2.1 Study KER-050-01

Several PD markers were explored in the phase 1 FIH trial in healthy postmenopausal women. In addition to effects on markers of hematopoiesis, elritercept was anticipated to suppress serum levels of FSH because of its effect on activin inhibition. Osteogenic precursors are also targets of KER-050-mediated inhibition of TGF- β superfamily ligands. BSAP is a glycoprotein found on the surface of osteoblasts (that is, bone-forming cells), is the earliest marker of bone formation, and is negatively regulated by activins ([Ikenoue et al. 1999](#)). As an activin ligand trap, elritercept was expected to increase BSAP. Over the course of the phase 1 trial (SAD and MAD), the following PD changes were observed:

- Hematologic parameters:
 - Rapid dose-dependent increases from baseline were observed in reticulocytes, Hgb, and RBCs following both single and multiple doses.
 - Increases in Hgb and RBCs were sustained for several weeks after a single dose of elritercept (beyond Day 42)
- Other PD effects:
 - FSH concentrations:
 - In elritercept-treated participants in Part 1, FSH levels decreased from baseline in the 0.05 mg/kg, 1.5 mg/kg, and 4.5 mg/kg dose groups, consistent with a potential suppression of FSH levels through activin inhibition.
 - Also in Part 1, in the elritercept 4.5 mg/kg dose group, FSH levels showed a sustained decrease over 15 days, and by Day 21, 66.7% of participants had a >40% decrease in FSH levels, suggestive of maximum activin inhibition at this time point.
 - In Part 2, multiple-dose administration of elritercept resulted in a decrease from baseline in mean FSH levels.
 - In both Part 1 and Part 2, increases in serum FSH were observed in placebo-treated participants.
 - Bone biomarkers:
 - In Part 1, serum levels of BSAP increased with increasing doses of elritercept and observed increases appeared to be dose related.
 - In Part 2, BSAP levels were elevated compared with placebo following multiple doses of elritercept.

- The trend toward a dose-dependent effect suggests potential effects on osteoblast activity, consistent with hypothesized target engagement.

5.2.2.2 Study KER050-MD-201

This trial evaluated ascending doses of elritercept (0.75 to 5.0 mg/kg) on markers of hematopoiesis (reticulocytes, Hgb, soluble transferrin receptor [sTfR], and platelets) in participants with LR-MDS with or without RS. Analyses of dose-related effects in the Part 1 Base Study show increases in reticulocytes and Hgb in all dose groups that were generally greater at higher doses. Increases in sTfR and platelets were also observed, but without any clear dose effect. Interpretation of dose effects on PD markers is limited in this trial by small cohort sizes and considerable heterogeneity among participants regarding baseline disease characteristics. To explore the relationships between elritercept and PD effects further, a PK/PD model was developed and is described in Section 5.2.1.2.

5.2.2.2.1 Pharmacodynamic Changes Related to Improvement of Anemia and Potential Effects Beyond Anemia in the MDS RP2D Population

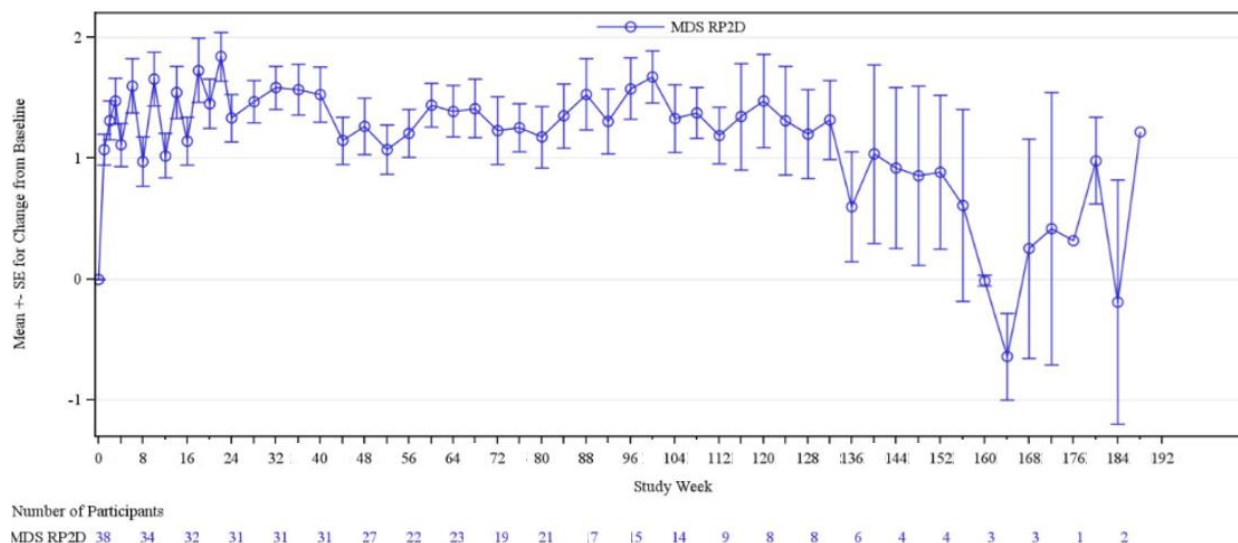
Changes in biomarkers summarized below support the potential for elritercept to improve anemia by restoring functional RBC production. They also support the potential for elritercept to address aspects of MDS disease biology beyond anemia, including iron homeostasis, multilineage hematopoiesis, osteoblast activity, and cardiac stress.

Pharmacodynamic Changes Related to Improvement of Anemia

Longitudinal changes in Hgb were assessed in LTB and NT RP2D participants to limit the confounding effect of RBC transfusions on the analysis. Mean increases in Hgb were observed that were sustained over time (Figure 5.a), supporting the potential for elritercept to durably restore functional erythropoiesis and treat anemia.

Similar sustained increases were observed when limiting the analysis to NT participants only, with mean (SD) increases in Hgb of 1.51 (0.805) g/dL at Week 24 (n=14), 1.26 (1.088) g/dL at Week 48 (n=10), 1.36 (0.892) g/dL at Week 72 (n=9), and 1.29 (0.942) d/dL at Week 96 (n=8).

Figure 5.a Hemoglobin (g/dL) Change from Baseline Over Time (MDS RP2D Population, LTB + NT Participants; Ongoing Study KER050-MD-201)



Source: Figure 14.2.4.8.LT

LTB: <4 units over 8 weeks prior to treatment.

X-axis labels (Study Week and Number of Participants) were modified from source for legibility

Baseline hemoglobin was calculated as average over the 8-week pretreatment period. Hemoglobin values within 14 days following a transfusion were censored except for pretransfusion values. Per protocol, the elritercept dose must be held at Hgb levels ≥ 12 g/dL. Number of participants at each timepoint is noted at the bottom of the figure.

Similarly, sTfR, a marker of erythropoietic activity, showed sustained increases in MDS RP2D participants over time. The mean increase in the MDS RP2D population at Week 24 was 34.05% (n=66), at Week 48 was 48.24% (n=49), at Week 72 was 43.45% (n=37), and at Week 96 was 54.77% (n=26). Sustained increases in sTfR in parallel to sustained increases in Hgb support the potential for elritercept to improve anemia by driving functional erythropoiesis.

Pharmacodynamic Changes Related to Potential Effects Beyond Anemia

Exploratory PD assessments support the potential for elritercept to not only treat anemia in participants with LR-MDS, but also to address the complex underlying biology of the disease more broadly. Changes in PD markers suggest benefits in reducing iron overload and improving iron homeostasis, addressing ineffective hematopoiesis across multiple cell lineages, restoring balance within the OHN, and potentially in improving cardiac strain.

- Sustained mean decreases in ferritin were observed in participants with baseline ferritin levels ≥ 1000 ng/mL, the threshold used by treatment guidelines to indicate iron overload (NCCN, 2024).
- Participants who achieved an erythroid response also showed, in aggregate, sustained increases in platelet count. Also, increases were observed among participants with baseline

CONFIDENTIAL

thrombocytopenia (platelets $<150 \times 10^9/L$), regardless of erythroid responder status; a total of 56.2% (50 of 89) of participants with baseline thrombocytopenia achieved a mean increase in platelets $\geq 30 \times 10^9/L$ sustained over any 8 week period on treatment.

- Sustained mean increases in BSAP, a marker of osteoblast activity, were observed in the overall MDS RP2D population regardless of hematologic response, baseline transfusion burden, or RS status. This is consistent with previous findings in healthy postmenopausal women (Section 5.3.2.1) and preclinical models which suggests the potential for elritercept to have an anabolic effect on bone.
- Preliminary exploration of changes in NT-proBNP suggest that elritercept treatment may be associated with improvements in cardiac strain, as evident by decreases in NT-proBNP over the course of the trial. Cardiac stress in patients with LR-MDS is exacerbated by chronic anemia, fluctuating hemodynamics due to transfusions, and iron overload. Elritercept inhibits activin A which directly contributes to inflammation-induced deterioration in the heart and is associated with heart failure (Phillips et al. 2009; Roh et al. 2019). Note that interpretation of the KER050-MD-201 NT proBNP dataset is limited due to the small amount of data available as of the DCO date.

5.2.2.3 Study KER050-MF-301

The Part 1 Dose Escalation portion of this trial evaluated ascending doses of elritercept (0.75 to 4.5 mg/kg). Interpretation of dose effects on PD markers is limited in this trial by small cohort sizes and considerable heterogeneity among participants with regard to baseline disease characteristics.

Several markers of erythropoiesis were evaluated in this trial. To prevent the confound of transfusions, PD data for sTfR, reticulocytes, and Hgb was examined in NTD participants pooled across the treatment arms (monotherapy and combination) to increase the sample size. However, it is important to note that despite being classified as NTD at baseline, several of these participants did receive transfusions, just not at amounts meeting the threshold of transfusion dependence based on IWG 2013. Increases in markers of erythropoiesis, including sTfR and reticulocytes, were observed over the first 12 weeks of treatment that were generally greater at higher dose levels (Table 5.d). There was not a clear dose relationship with Hgb, potentially due to general variability of Hgb response across dose cohorts as well as differences in evaluable post-baseline Hgb data due to ongoing transfusions.

Table 5.d Average Change in Markers of Erythropoiesis Over the First 8 or 12 Weeks During the Study by Dose Level (Part 1 Dose Escalation, NTD Participants)

Biomarkers	Elritercept 0.75 mg/kg	Elritercept 1.5 mg/kg	Elritercept 3.0 mg/kg	Elritercept 4.5 mg/kg
sTfR, mean (SEM), mg/mL	n=7	n=4	n=6	n=6
	-0.05 (0.251)	0.23 (0.147)	0.45 (0.123)	0.80 (0.225)

Table 5.d Average Change in Markers of Erythropoiesis Over the First 8 or 12 Weeks During the Study by Dose Level (Part 1 Dose Escalation, NTD Participants)

Biomarkers	Elritercept 0.75 mg/kg	Elritercept 1.5 mg/kg	Elritercept 3.0 mg/kg	Elritercept 4.5 mg/kg
Reticulocytes, mean (SEM), $\times 10^9/L$	n=6 8.69 (3.316)	n=4 8.48 (13.275)	n=5 30.18 (18.557)	n=6 38.59 (11.096)
Hgb, mean (SEM), g/dL	n=4 0.66 (0.411)	n=5 1.22 (0.609)	n=3 1.17 (0.200)	n=5 0.56 (0.311)

Source Ad hoc Table 18 and Ad hoc Table 18.1

Participants were only included in the analysis if they had at least 12 weeks postbaseline data for reticulocytes and Hgb or 8 weeks for sTfR, leading to different numbers of participants across biomarkers.

Preliminary assessment of longitudinal changes in Hgb for all NTD participants in Parts 1 and 2 demonstrated mean increases in both the monotherapy and combination arms that were generally maintained over 24 weeks.

Observed changes in platelet count suggest that platelet levels were generally maintained if not improved, particularly among participants in the combination arm. At baseline, median platelet counts were below the lower limit of normal in both arms. To explore platelet changes among participants who were thrombocytopenic at baseline, the maximum change in platelets over any 12-week period within the first 24 weeks was assessed. Of the 18 participants (9 in each arm) who had platelet counts $<150 \times 10^9/L$ at baseline and at least 12 weeks of post-baseline platelet data, 3 participants (1 in monotherapy and 2 in combination) showed a mean increase in platelet count $\geq 30 \times 10^9/L$ over a 12-week period during the first 24 weeks. Smaller increases were observed in 5 other participants in the combination arm and the remaining evaluable participants either showed minimal change or decreases that were generally $<30 \times 10^9/L$. Biomarkers potentially indicative of effects beyond anemia were not yet mature enough for analysis as of the data cutoff.

5.2.2.4 Pharmacodynamic Conclusions

Several PD markers were assessed to understand the effects of elritercept on target signaling pathways and tissues as well as effects in stimulating hematopoiesis. In general, observed changes in PD markers were consistent with those expected following inhibition of ActRIIA ligands and supported a mechanism whereby elritercept can promote differentiation and maturation of both erythroid and megakaryocyte progenitors. Also, PD changes generally showed dose effects, however, interpretation of dose effects in Study KER050-MD-201 and KER050-MF-301 is limited by small cohort sizes and considerable heterogeneity among participants with regard to baseline disease characteristics.

After treatment with elritercept, the following key PD effects were observed:

In healthy postmenopausal women:

CONFIDENTIAL

- Rapid, dose-dependent increases in reticulocytes, RBCs, and Hgb were observed following a single dose
- Increases in RBCs and Hgb were sustained beyond Day 42 following a single dose suggesting potential not only to stimulate release of late-stage erythroid precursors but potentially to support continued propagation of precursors along the erythroid pathway
- Decreases from baseline in FSH concentrations in elritercept-treated groups compared with increases in FSH concentrations in placebo-treated participants is indicative of activin inhibition. Increases from baseline in BSAP in healthy postmenopausal women were also observed and trended toward a dose-dependence effect, suggesting potential effects on osteoblast activity, consistent with activin inhibition.

In participants with MDS (Study KER050-MD-201):

- In the Part 1 Base Study increases in reticulocytes and Hgb were observed in all dose groups that were generally greater at higher dose levels.
- Increases in sTfR and platelets were also observed, but without any clear dose effect.
- Additional PD changes support potential of elritercept to address MDS biology beyond anemia including iron overload and iron homeostasis, hematopoiesis across multiple cell lineages, multiple components of the OHN, and cardiac strain (as presented in Section 5.2.2.2).

In participants with MF (Study KER050-MF-301):

- PD changes in markers of hematopoiesis support potential for elritercept to improve anemia while preserving or improving platelet counts:
 - Mean increases in Hgb were observed in both arms that were generally maintained over 24 weeks.
 - Platelet counts were generally maintained or improved, particularly in the combination arm; improvements were observed over 12 weeks within the first 24 weeks of treatment for participants who were thrombocytopenic at baseline, even in combination with ruxolitinib.

5.2.3 Immunogenicity

5.2.3.1 Study KER-050-01

Overall, 3 out of 38 (7.9%) elritercept-treated participants had at least 1 positive test result in the ADA confirmatory assay. All these 3 participants were from Part 1 (SAD); 1 participant (12.5%) administered 0.5 mg/kg tested positive at Day 15 with an ADA titer of 1:4; 1 participant (16.7%) administered 4.5 mg/kg tested positive at Day 15 with an ADA titer of 1:64; and 1 participant (12.5%) administered 1.5 mg/kg tested positive at the end of study (Day 84) with an ADA titer of 1:16. Neither participant who had a confirmed positive result at Day 15 was confirmed positive at the end of study (Day 84). One participant who had no assessment on Day 15, had a

confirmed positive at the end of study (Day 84) but tested negative on follow-up assessment after end of study.

In an evaluation of potential impact of positive ADA titers on PK exposure, 1 participant exhibited the lowest exposure (both C_{max} and AUC_{last}) of participants in that dose group, with exposure values approximately 50% lower than the group mean. However, serum elritercept exposure in the other 2 participants who had higher antibody titer values was within 1 standard deviation of the group mean for that dose cohort. While an impact of positive ADA titer on PK exposure cannot be conclusively ruled out, it was considered to be unlikely in this trial.

5.2.3.2 Study KER050-MD-201

Twenty-four of 107 (22.4%) immunogenicity-evaluable participants had at least 1 positive test result in the ADA confirmatory assay as of the DCO date.

Five (4.7%) of these participants had a positive test result at baseline (preexisting ADA per prespecified analysis). Of these 4 participants, 3 had negative results in the ADA assay post-baseline and 2 had positive post-baseline titers <4-fold of the titer at baseline.

Nineteen of 107 (17.8%) participants had a positive test result on study treatment (treatment-emergent ADA per prespecified analysis). Of these 19 participants, 18 had a negative test result in the ADA assay at baseline and 1 had a positive post-baseline titer $\geq$ 4-fold of the titer at baseline. There was no obvious relationship between the dose level of elritercept and the propensity for an ADA-positive test result.

Overall, low rates of ADA positivity were observed, and, in most cases, elritercept concentrations were not impacted by ADA positivity.

5.2.3.3 Study KER050-MF-301

Monotherapy

Four of 34 (11.8%) participants had at least 1 positive test result in the ADA confirmatory assay as of the DCO date.

One (2.9%) of these participants had a positive test result at baseline (preexisting ADA per prespecified analysis). This participant had positive post-baseline titers <4-fold of baseline titer.

Three of 34 (8.8%) participants had a positive test result on study treatment (treatment-emergent ADA per prespecified analysis). All of these 3 participants had a negative test result in the ADA assay at baseline. There was no obvious relationship between the dose level of elritercept and the propensity for an ADA-positive test result.

Combination Therapy

Three of 57 (5.3%) participants had at least 1 positive test result in the ADA confirmatory assay as of the DCO date.

Two (3.5%) of these participants had a positive test result at baseline (preexisting ADA per prespecified analysis) and had positive post-baseline titers <4-fold of baseline titer.

None of the participants in the combination arm had a positive test result on study treatment.

5.3 Clinical Safety

To date, elritercept has been generally well tolerated based on data from the completed Keros-initiated studies Study KER 050-01 in healthy postmenopausal women (5.3.1), the ongoing Study KER050-MD-201 (5.3.2), Study KER050-MF-301 (5.3.4) in participants with LR-MDS/CMML and MF, respectively, and the Hansoh-initiated trial, Study HS-20106-201 (5.3.3).

Elritercept clinical studies evaluate different trial populations and indications; trial designs include various elritercept dosing regimens, including monotherapy or in combination with ruxolitinib. To provide context for data interpretation, safety data are presented separately for each trial. All data for ongoing studies should be regarded as preliminary and not final.

Safety data are focused on AEs that were treatment-emergent in the completed and ongoing studies of elritercept. AEs were coded using MedDRA version 23.0 or higher and are summarized by SOC and/or PT. Laboratory data are not presented in safety sections unless excursions in laboratory values were reported as TEAEs.

5.3.1 Study KER-050-01

Single (over the 0.05 mg/kg to 4.5 mg/kg dose range) and multiple (2 doses at 0.75 mg/kg) doses of elritercept were well tolerated in healthy postmenopausal women in phase 1 Study KER-050-01. The proportions of participants with ≥ 1 TEAE were similar between elritercept and placebo groups. Overall, 32 out of 38 (84.2%) elritercept-treated participants experienced ≥ 1 TEAE. The most common ($\geq 10\%$ participants) TEAEs reported by elritercept-treated participants by MedDRA PT were haemoglobin increased and headache (31.6% each), and hypertension, nausea, and upper respiratory tract infection (10.5% each). All TEAEs were mild or moderate in severity and there were no DLTs.

The most frequently reported treatment-related TEAEs in elritercept-treated participants were haemoglobin increased (31.6%), headache (23.7%), hypertension (10.5%), and nausea, vomiting and injection site reactions (7.9% each). Hypertension occurred only in participants who received 4.5 mg/kg. These events were mild, transient, and associated with increase in Hgb. Observed TEAEs of haemoglobin increased and hypertension are consistent with the known pharmacological activity of elritercept on increasing RBC production. injection-site reactions (injection site erythema and injection site pain) were reported by 3 participants that received 2 doses at 0.75 mg/kg. In 2 participants, the injection site reactions were reported after the second dose and in 1 participant, the injection site reaction was reported after the first dose. All injection-site reactions were either mild or moderate, and resolved without any treatment.

No elritercept-treated participant had Grade ≥ 3 TEAEs or TESAEs. There were neither TEAEs leading to discontinuation nor fatal TEAEs.

A total of 3 out of 38 (7.9%) elritercept-treated participants that had a positive ADA test result on a single occasion experienced influenza-like illness, hypertension, and headache, post-positive ADA test result. These events can be signs/symptoms of an immunologic reaction; however, these occurred more frequently in participants who had negative ADA test results than in participants who had positive ADA test results.

5.3.2 Study KER050-MD-201

Safety data from Study KER050-MD-201 presented in this IB are from the LTS analysis set Section 5.1.1.2, which combines participants from Parts 1 and 2 of the trial (total participants with either MDS or CMML; n=109). The LTS analysis set represents the most comprehensive pool of participants for assessing the safety profile of elritercept in Study KER050-MD-201.

While increases in HgB and platelet levels are considered supportive of the proposed mechanism of action of elritercept to increase RBC and platelet production, they are also closely monitored for safety. Both parameters are evaluated prior to dosing to assess for values or increases that exceed thresholds that meet protocol-specified criteria for dose delay or reduction. As of the DCO date, 15 participants (13.8%) had experienced dose delays due to increased Hgb; no participants had experienced dose delay due to increased platelets. One participant (0.9%) discontinued study treatment due to increased platelets; no participants discontinued study treatment due to increased HgB.

5.3.2.1 Study KER050-MD-201: Extent of Exposure

As of the DCO date, median duration of exposure to elritercept was 12.55 months (range 0.9, 45.3). A total of 85 (78.0%) participants had ≥ 6 months of exposure, 57 (52.3%) had ≥ 12 months of exposure, and 27 (24.8%) had ≥ 24 months of exposure.

5.3.2.2 Study KER050-MD-201: AEs

5.3.2.2.1 Study KER050-MD-201: TEAEs

Overall, 108 out of 109 (99.1%) participants experienced ≥ 1 TEAE. No DLTs have been reported. Treatment-related TEAEs of any grade were reported by 50 (45.9%) participants, of which Grade ≥ 3 TEAEs were reported by 6 (5.5%) participants. TESAEs were reported by 56 (51.4%) participants, of which treatment-related TESAEs were reported by 4 (3.7%) participants. Nineteen (17.4%) participants discontinued study treatment because of TEAEs as of the DCO date. Fatal TEAEs were reported by 6 (5.5%) participants; all of these fatal TEAEs were assessed as not related to study treatment.

An overview of TEAEs reported are shown in [Table 5.e](#).

Table 5.e Overview of TEAEs – LTS (Safety Population; Study KER050-MD-201)

	MDS RP2D N=96 n (%)	MDS Low Dose N=6 n (%)	MDS Total N=102 n (%)	CMML N=7 n (%)	Total MDS + CMML N=109 n (%)
Any TEAE	95 (99.0)	6 (100)	101 (99.0)	7 (100)	108 (99.9)
Any Treatment-Related TEAE	44 (45.8)	3 (50.0)	47 (46.1)	3 (42.9)	50 (45.9)
Any DLT	0	0	0	0	0
Any TESAЕ	49 (51.0)	4 (66.7)	53 (52.0)	3 (42.9)	56 (51.4)
Any Treatment-Related TESAЕ	4 (4.2)	0	4 (3.9)	0	4 (3.7)
Any TEAE Leading to Death	5 (5.2)	1 (16.7)	6 (5.9)	0	6 (5.5)
Any TEAE Leading to Treatment Discontinuation	17 (17.7)	1 (16.7)	18 (17.6)	1 (14.3)	19 (17.4)
Any TEAE Leading to Dose Modification	25 (26.0)	1 (16.7)	26 (25.5)	1 (14.3)	27 (24.8)
Any Grade ≥ 3 TEAE	57 (59.4)	4 (66.7)	61 (59.8)	5 (71.4)	66 (60.6)
Any Treatment-Related Grade ≥ 3 TEAE	5 (5.2)	0	5 (4.9)	1 (14.3)	6 (5.5)

Source: Table 14.3.1.1.LT; Table 14.3.1.7.LT

The first dose of study drug was C1D1 except for Part 1 participants with treatment interruption, whose C1D1 was redefined relative to the dose date at C5D1. The grouping of dose level was based on the highest dose levels received.

The most frequently reported ($\geq 15\%$ participants) TEAEs by MedDRA PT included diarrhoea (30 participants, 27.5%), fatigue (29 participants, 26.6%), COVID-19 (23 participants, 21.1%), anaemia (21 participants, 19.3%), dizziness, epistaxis, nausea, (19 participants, 17.4% each), dyspnoea (18 participants, 16.5%), and constipation, fall, and oedema peripheral, (17 participants, 15.6% each). Most TEAEs were reported by one (0.9%) participant each.

TEAEs reported in $\geq 10\%$ of all participants are provided below in [Table 5.f](#).

Table 5.f TEAEs Reported in ≥10% of Total Participants by Preferred Term in LTS (Safety Population, Study KER050-MD-201)

Preferred Term	MDS RP2D (N=96) n (%)	MDS Low Dose (N=6) n (%)	MDS Total (N=102) n (%)	CMML (N=7) n (%)	Total MDS + CMML (N=109) n (%)
Participants with at least 1 TEAE	95 (99.0)	6 (100)	101 (99.0)	7 (100)	108 (99.1)
Diarrhoea	28 (29.2)	0	28 (27.5)	2 (28.6)	30 (27.5)
Fatigue	27 (28.1)	2 (33.3)	29 (28.4)	0	29 (26.6)
COVID-19	22 (22.9)	0	22 (21.6)	1 (14.3)	23 (21.1)
Anaemia	19 (19.8)	2 (33.3)	21 (20.6)	0	21 (19.3)
Dizziness	18 (18.8)	1 (16.7)	19 (18.6)	0	19 (17.4)
Epistaxis	17 (17.7)	1 (16.7)	18 (17.6)	1 (14.3)	19 (17.4)
Nausea	19 (19.8)	0	19 (18.6)	0	19 (17.4)
Dyspnoea	17 (17.7)	1 (16.7)	18 (17.6)	0	18 (16.5)
Constipation	14 (14.6)	2 (33.3)	16 (15.7)	1 (14.3)	17 (15.6)
Fall	17 (17.7)	0	17 (16.7)	0	17 (15.6)
Oedema peripheral	15 (15.6)	2 (33.3)	17 (16.7)	0	17 (15.6)
Cough	12 (12.5)	1 (16.7)	13 (12.7)	2 (28.6)	15 (13.8)
Hypertension	13 (13.5)	0	13 (12.7)	2 (28.6)	15 (13.8)
Urinary tract infection	14 (14.6)	0	14 (13.7)	1 (14.3)	15 (13.8)
Asthenia	12 (12.5)	0	12 (11.8)	2 (28.6)	14 (12.8)
Arthralgia	12 (12.5)	1 (16.7)	13 (12.7)	0	13 (11.9)
Headache	12 (12.5)	0	12 (11.8)	1 (14.3)	13 (11.9)
Back pain	11 (11.5)	0	11 (10.8)	1 (14.3)	12 (11.0)
Vomiting	11 (11.5)	0	11 (10.8)	0	11 (10.1)

Source: Table 14.3.1.4.LT

AEs were coded with MedDRA Dictionary version 23.0. The first dose of study drug was C1D1 except for Part 1 participants with treatment interruption, whose C1D1 was redefined relative to the dose date at C5D1. The grouping of dose level was based on the highest dose levels received.

As noted in [Table 5.f](#), several symptoms commonly associated with MDS, including fatigue/asthenia, dyspnoea, and dizziness were very common TEAEs reported by the trial participants.

5.3.2.2.2 Study KER050-MD-201: Treatment-Related TEAEs

TEAEs that were assessed as related to study treatment by the treating Investigator, by MedDRA PT, reported by ≥2% of participants included nausea (7 participants, 6.4%); diarrhoea (6 participants, 5.5%); injection site reaction (5 participants, 4.6%); headache and hypertension (4 participants, 3.7% each); and ALT increased, AST increased, asthenia, dizziness, fatigue, and

neutropenia, (3 participants, 2.8% each). Most treatment-related TEAEs were reported by 1 (0.9%) participant each.

TEAEs assessed as related to study treatment reported in $\geq 1\%$ of participants are provided below in Table 5.g.

Table 5.g Treatment-Related TEAEs Reported in $\geq 1\%$ Participants of Total Participants by Preferred Term – LTS (Safety Population; Study KER050-MD-201)

Preferred Term	MDS RP2D N=96 n (%)	MDS Low Dose N=6 n (%)	MDS Total N=102 n (%)	CMML N=7 n (%)	Total MDS + CMML N=109 n (%)
Participants with at least 1 treatment-related TEAE	44 (45.8)	3 (50.0)	47 (46.1)	3 (42.9)	50 (45.9)
Nausea	7 (7.3)	0	7 (6.9)	0	7 (6.4)
Diarrhoea	6 (6.3)	0	6 (5.9)	0	6 (5.5)
Injection site reaction	4 (4.2)	0	4 (3.9)	1 (14.3)	5 (4.6)
Headache	4 (4.2)	0	4 (3.9)	0	4 (3.7)
Hypertension	3 (3.1)	0	3 (2.9)	1 (14.3)	4 (3.7)
Alanine aminotransferase increased	3 (3.1)	0	3 (2.9)	0	3 (2.8)
Aspartate aminotransferase increased	3 (3.1)	0	3 (2.9)	0	3 (2.8)
Asthenia	3 (3.1)	0	3 (2.9)	0	3 (2.8)
Dizziness	3 (3.1)	0	3 (2.9)	0	3 (2.8)
Neutropenia	3 (3.1)	0	3 (2.9)	0	3 (2.8)
Blood alkaline phosphatase increased	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Blood bilirubin increased	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Constipation	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Decreased appetite	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Dyspnoea	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Injection site pain	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Lethargy	1 (1.0)	1 (16.7)	2 (2.0)	0	2 (1.8)
Pruritus	2 (2.1)	0	2 (2.0)	0	2 (1.8)

AEs were coded with MedDRA Dictionary version 23.0. The first dose of study drug was C1D1 except for Part 1 participants with treatment interruption, whose C1D1 was redefined relative to the dose date at C5D1. The grouping of dose levels was based on the highest dose levels received.

Source: Table 14.3.1.6.LT

ISRs were reported in a total of 15 (13.8%) participants, which included PTs of injection site reaction by 7(6.4%) participants, injection site pain by 3 (2.8%) participants, and injection site bruising, injection site erythema, injection site haemorrhage, injection site pruritus, and injection site swelling by 1 (0.9%) participant each.

The observed ISRs were localized, mild to moderate in severity, lasted for 1 to <55 days, and all but 1 event (which began ~30 days before the DLP) resolved over time. One (0.9%) participant experienced 2 TESAEs of injection site reaction that were assessed as related to study treatment.

5.3.2.2.3 Study KER050-MD-201: TEAEs of Grade ≥ 3

Grade ≥ 3 TEAEs were reported in a total of 66 (60.6%) participants [Table 5.e]. Grade ≥ 3 TEAEs reported by $\geq 2\%$ participants by MedDRA PT included anaemia (14 participants, 12.8%); hypertension (6 participants, 5.5%); dyspnoea, neutropenia, neutrophil count decreased, and pneumonia (5 participants, 4.6% each); and atrial fibrillation, acute myocardial infarction, fall, syncope, and vomiting (3 participants, 2.8%). Most Grade ≥ 3 TEAEs were reported by one (0.9%) participant each.

A total of 8 treatment-related Grade ≥ 3 TEAEs were reported by 6 (5.5%) participants. These treatment-related Grade ≥ 3 TEAEs were reported by one (0.9%) participant each and included the PTs of adenocarcinoma gastric, anaemia, dyspnoea, headache, hypertension, neutropenia, neutrophil count decreased, and syncope.

5.3.2.2.4 Study KER050-MD-201: TESAEs

TESAEs were reported in a total of 56 (51.4%) participants. TESAEs reported by $\geq 1\%$ of participants by MedDRA PT included anaemia (6 participants, 5.5%); pneumonia (5 participants, 4.6%); dyspnoea (4 participants, 3.7%); syncope (3 participants, 2.8%) and by 2 (1.8%) participants each were: acute myocardial infarction, chronic obstructive pulmonary disease, epistaxis, fall, gastroenteritis, inguinal hernia, spinal compression fracture, squamous cell carcinoma of skin, and viral infection. Most TESAEs were reported by only one (0.9%) participant.

Treatment-related TESAEs were reported for 4 (3.7%) participants. All of these treatment-related TESAEs (adenocarcinoma gastric, dyspnoea; injection site reaction, and syncope) and were reported for 1 (0.9%) participant each.

5.3.2.2.5 Study KER050-MD-201: TEAEs leading to Death

Treatment-emergent deaths occurred in 6 (5.5%) participants due to fatal TEAEs of cardiac failure, idiopathic pulmonary fibrosis, myocardial infarction, non-Hodgkin lymphoma, obesity cardiomyopathy, and sudden death, all of which were assessed as not related to study treatment.

5.3.2.2.6 Study KER050-MD-201: TEAEs Leading to Dose Interrupted

TEAEs leading to dose interruption were reported for a total of 26 (23.9%) participants (Table 5.h). TEAEs leading to dose interruption in ≥ 2 (1.8%) participants included

COVID-19 (5 participants, 4.6%), anaemia and hypertension (3 participants, 2.8% each), and dyspnoea, gastroenteritis, and white coat hypertension (2 participants, 1.8% each).

Table 5.h TEAEs Leading to Dose Interrupted by SOC and PT in LTS (Safety Population: Study KER50-MD-201)

System Organ Class Preferred Term	MDS RP2D (N=96) n (%)	MDS Low Dose (N=6) n (%)	MDS Total (N=102) n (%)	CMML (N=7) n (%)	Total MDS + CMML (N=109) n (%)
Participants with at least 1TEAE	24 (25.0)	1 (16.7)	25 (24.5)	1 (14.3)	26 (23.9)
Infections and infestations	8 (8.3)	0	8 (7.8)	0	8 (7.3)
COVID-19	5 (5.2)	0	5 (4.9)	0	5 (4.6)
Gastroenteritis	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Pneumonia	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Pneumonia staphylococcal	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Respiratory tract infection	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Upper respiratory tract infection	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Vascular disorders	5 (5.2)	0	5 (4.9)	1 (14.3)	6 (5.5)
Hypertension	3 (3.1)	0	3 (2.9)	0	3 (2.8)
White coat hypertension	1 (1.0)	0	1 (1.0)	1 (14.3)	2 (1.8)
Orthostatic hypotension	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Blood and lymphatic system disorders	4 (4.2)	0	4 (3.9)	0	4 (3.7)
Anaemia	3 (3.1)	0	3 (2.9)	0	3 (2.8)
Haemolysis	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Injury, poisoning and procedural complications	4 (4.2)	0	4 (3.9)	0	4 (3.7)
Facial bones fracture	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Fall	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Joint dislocation	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Thermal burn	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Gastrointestinal disorders	3 (3.1)	0	3 (2.9)	0	3 (2.8)
Gastritis	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Inguinal hernia	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Pancreatitis	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Cardiac disorders	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Acute myocardial infarction	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Atrial fibrillation	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Supraventricular tachycardia	1 (1.0)	0	1 (1.0)	0	1 (0.9)
General disorders and administration site conditions	1 (1.0)	1 (16.7)	2 (2.0)	0	2 (1.8)
Non-cardiac chest pain	1 (1.0)	0	1 (1.0)	0	1 (0.9)

Table 5.h TEAEs Leading to Dose Interrupted by SOC and PT in LTS (Safety Population: Study KER50-MD-201)

System Organ Class Preferred Term	MDS RP2D (N=96) n (%)	MDS Low Dose (N=6) n (%)	MDS Total (N=102) n (%)	CMML (N=7) n (%)	Total MDS + CMML (N=109) n (%)
Pyrexia	0	1 (16.7)	1 (1.0)	0	1 (0.9)
Respiratory, thoracic and mediastinal disorders	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Dyspnoea	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Hepatobiliary disorders	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Jaundice cholestatic	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Investigations	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Haemoglobin increased	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Metabolism and nutrition disorders	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Hyponatraemia	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Musculoskeletal and connective tissue disorders	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Arthritis	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Adenocarcinoma gastric	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Social circumstances	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Social problem	1 (1.0)	0	1 (1.0)	0	1 (0.9)

Source: Table 14.3.1.11.2.LT

AEs were coded with MedDRA Dictionary Version 23.0.

TEAE was defined as AE that commenced on or after the first dose of elritercept and within 60 days after the last dose of elritercept, or analysis cutoff date, whichever is earlier. The first dose of elritercept was C1D1 except for Part 1 participants with treatment interruption, whose C1D1 was redefined relative to the dose date at C5D1.

If a participant experienced more than 1 event with a given SOC or PT within SOC, that participant was counted only once for that category.

The grouping of dose level was based on the highest dose levels received.

TEAEs leading to dose reduction were reported for a total of 3 participants ([Table 5.i](#)) and included the PTs of neutropenia (2 participants, 1.8%) and weight decreased (1 participant, 1.8%).

Table 5.i TEAEs Leading to Dose Reduced by SOC and PT in LTS (Safety Population: Study KER50-MD-201)

System Organ Class Preferred Term	MDS RP2D (N=96) n (%)	MDS Low Dose (N=6) n (%)	MDS Total (N= 102) n (%)	CMML (N=7) n (%)	Total MDS + CMML (N=109) n (%)
Participants with at least 1TEAE	3 (3.1)	0	3 (2.9)	0	3 (2.8)
Blood and lymphatic system disorders	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Neutropenia	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Investigations	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Weight decreased	1 (1.0)	0	1 (1.0)	0	1 (0.9)

Source: Table 14.3.1.11.1.LT

AEs were coded with MedDRA Dictionary Version 23.0.

TEAE was defined as AE that commenced on or after the first dose of elritercept and within 60 days after the last dose of elritercept, or analysis cutoff date, whichever is earlier. The first dose of elritercept was C1D1 except for Part 1 participants with treatment interruption, whose C1D1 was redefined relative to the dose date at C5D1.

If a participant experienced more than 1 event with a given SOC or PT within SOC, that participant was counted only once for that category.

The grouping of dose level was based on the highest dose levels received.

TEAEs leading to discontinuation of study treatment were reported in a total of 19 (17.4%) participants (Table 5.j). Of these, only dyspnoea was reported for 2 (1.8%) participants. All other PTs were reported for 1 (0.9%) participant only and included acute myeloid leukaemia, adenocarcinoma [CMML], cardiac failure, cardiac failure congestive, chronic obstructive pulmonary disease, dementia Alzheimer's type, diffuse large B-cell lymphoma, diverticulitis, gastrointestinal disorder, idiopathic pulmonary fibrosis, injection site reaction, lung adenocarcinoma, lymphocytic leukaemia, myocardial infarction, nodular melanoma, non-Hodgkin lymphoma, non-small cell lung cancer, obesity cardiomyopathy, platelet count increased, and sudden death.

Table 5.j TEAEs Leading to Discontinuation of Investigational Medicinal Product by SOC and PT in LTS (Safety Population; Study KER50-MD-201)

System Organ Class Preferred Term	MDS RP2D (N=96) n (%)	MDS Low Dose (N=6) n (%)	MDS Total (N=102) n (%)	CMML (N=7) n (%)	Total MDS + CMML (N=109) n (%)
Participants with at least one TEAE	17 (17.7)	1 (16.7)	18 (17.6)	1 (14.3)	19 (17.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (7.3)	0	7 (6.9)	1 (14.3)	8 (7.3)
Acute myeloid leukaemia	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Adenocarcinoma	0	0	0	1 (14.3)	1 (0.9)
Diffuse large B-cell lymphoma	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Lung adenocarcinoma	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Lymphocytic leukaemia	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Nodular melanoma	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Non-Hodgkin lymphoma	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Non-small cell lung cancer	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Cardiac disorders	3 (3.1)	1 (16.7)	4 (3.9)	0	4 (3.7)
Cardiac failure	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Cardiac failure congestive	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Myocardial infarction	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Obesity cardiomyopathy	0	1 (16.7)	1 (1.0)	0	1 (0.9)
Respiratory, thoracic and mediastinal disorders	4 (4.2)	0	4 (3.9)	0	4 (3.7)
Dyspnoea	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Chronic obstructive pulmonary disease	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Idiopathic pulmonary fibrosis	1 (1.0)	0	1 (1.0)	0	1 (0.9)
General disorders and administration site conditions	2 (2.1)	0	2 (2.0)	0	2 (1.8)
Injection site reaction	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Sudden death	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Gastrointestinal disorders	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Gastrointestinal disorder	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Diverticulitis	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Investigations	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Platelet count increased	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Nervous system disorders	1 (1.0)	0	1 (1.0)	0	1 (0.9)
Dementia Alzheimer's type	1 (1.0)	0	1 (1.0)	0	1 (0.9)

Table 5.j TEAEs Leading to Discontinuation of Investigational Medicinal Product by SOC and PT in LTS (Safety Population; Study KER50-MD-201)

System Organ Class Preferred Term	MDS RP2D (N=96) n (%)	MDS Low Dose (N=6) n (%)	MDS Total (N=102) n (%)	CMML (N=7) n (%)	Total MDS + CMML (N=109) n (%)
--------------------------------------	--------------------------------	-----------------------------------	----------------------------------	------------------------	--

Source: Table 14.3.2.3.LT

AEs were coded with MedDRA Dictionary Version 23.0.

TEAE was defined as AE that commenced on or after the first dose of elritercept and within 60 days after the last dose of elritercept, or analysis cutoff date, whichever is earlier. The first dose of elritercept was C1D1 except for Part 1 participants with treatment interruption, whose C1D1 was redefined relative to the dose date at C5D1.

If a participant experienced more than 1 event with a given SOC or PT within SOC, that participant was counted only once for that category.

The grouping of dose level was based on the highest dose levels received.

With the exception of Grade 3 dyspnoea, Grade 2 injection site reaction, and Grade 2 platelet count increased (1 event each), all these events were assessed as not related to study treatment by the investigator. Most of these events were related to worsening of concomitant comorbid conditions.

5.3.2.2.7 Study KER050-MD-201: TEAEs in Participants with Positive ADA

Of the 24 participants who had ADA-positive results, ≥ 1 TEAE was reported by 22 (91.7%) participants. The most frequently reported ($\geq 10\%$, 3 participants) TEAEs included nausea (5 participants, 20.8%), fall, anaemia, urinary tract infection, constipation, Back pain (4 participants, 16.7%); COVID-19, dyspnoea, lethargy, dizziness, oedema peripheral, and vomiting (3 participants, 12.5% each). Most of these TEAEs were reported by one (4.2%) participant each.

One of the participants experienced 2 TESAEs of injection site reaction that were assessed as related to study treatment. This participant received study treatment in the Part 1 Base Study (Process I; 0.75 mg/kg) and was enrolled in the Part 1 Extension Period in the LTS (Process II; 3.75 mg/kg) after a significant treatment gap because of administrative reasons. Initially, the participant experienced Grade 2 injection site reaction (pain and erythema), requiring hospitalization after 11 days of study drug administration (first dose of 3.75 mg/kg in the Part 1 Extension Period) and resolved with antibiotics and antihistamine therapy. The participant continued study treatment at the same dose of 3.75 mg/kg in the next cycle and experienced Grade 2 injection site reaction (erythema with pain and induration) 2 days after receiving study drug. This episode resolved after administration of antibiotics and steroid therapy and the participant permanently discontinued study treatment thereafter. The participant tested negative for ADA at all points of sampling during the Part 1 Base Study (predose Cycles 1 through 4) but subsequently tested positive for ADA.

5.3.2.2.8 Study KER050-MD-201: Electrocardiogram (ECG) Corrected QT Interval (QTc) Prolongation

Based on the review of ECG and cardiac event data, there is no evidence emerging from this trial suggesting that elritercept has the potential to prolong the QT interval.

Among 91 participants with evaluable Fridericia corrected QT interval (QTcF) results, only 5 (5.5%) had QTcF readings >480 ms and ≤ 500 ms, and 1 (1.1%) had QTcF readings >500 ms corresponding to Common Terminology Criteria for AEs Grade 2 prolonged corrected QT interval (QTc), none of which was assessed as clinically significant by the investigator.

Based on the review of ECG and cardiac event data, there is no evidence emerging from Study KER050-MD-201 suggesting that elritercept has proarrhythmic potential. Additionally, being a large biological protein, elritercept does not directly inhibit the human ether-a-go-go related gene (hERG) channel. Nonclinical data, including NHP toxicology studies have demonstrated no substantial changes in ECG parameters. There were no clinically significant ECG changes in healthy participants in the phase 1 Study KER-050-01. In addition, using a concentration-response analysis, there was no evidence that increasing concentrations of elritercept lead to increases in $\Delta\Delta\text{QTc}$ or ΔQTc in either healthy participants (KER-050-01) or patients with MDS (KER-050-MD-201), respectively (FDA. (2022). Guidance for Industry: E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential — Questions and Answers. US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); Garnett et al., 2018). Taken together, the data demonstrate that the risk of elritercept to lead to QT interval/QTc prolongation and proarrhythmic potential is considered low.

5.3.3 Study HS-20106-201

As described in Section 5.1.1.3, Study HS-20106-201 is a phase 2, 2-part trial evaluating safety, PK, and efficacy of HS-20106 in adult participants with very low/low/intermediate-risk MDS with anemia in the territory of mainland China. As of 03 April 2025, 11 participants have been enrolled. Overall, 6 (54.5%) participants have experienced ≥ 1 TEAE (Table 5.k), with only Influenza-like illness, platelet count decreased, and white blood cell count decreased reported for ≥ 2 participants (Table 5.l). Grade 3 events include platelet count decreased (2 participants) and white blood cell count decreased (1 participant): these Grade 3 TEAEs were assessed as related to treatment. No TEAEs leading to treatment discontinuation and no TESAEs have been reported.

Table 5.k Overview of TEAEs (Study HS-20106-201)

	N=11 n (%)
Any TEAE	6 (54.5)
Any Treatment-Related TEAE	2 (18.2)
Any TESAE	0
Any Treatment-Related TESAE	0
Any TEAE Leading to Death	0
Any TEAE Leading to Treatment Discontinuation	0
Any Grade ≥ 3 TEAE	2 (18.2)
Any Treatment-Related Grade ≥ 3 TEAE	2 (18.2)

Source: Hansoh Table 2

Table 5.l TEAEs by Preferred Term (Study HS-20106-201)

Preferred Term	N=11 n (%)
Participants with at least 1 TEAE	6 (54.5)
Influenza like illness	3 (27.3)
Platelet count decreased	2 (18.2)
White blood cell count decreased	2 (18.2)
Alanine aminotransferase increased	1 (9.1)
Aspartate aminotransferase increased	1 (9.1)
Cholecystitis	1 (9.1)
Eyelid oedema	1 (9.1)
Hypertriglyceridaemia	1 (9.1)
Hyperuricaemia	1 (9.1)
Neutrophil count decreased	1 (9.1)
Oedema peripheral	1 (9.1)
Pyrexia	1 (9.1)
Urinary tract infection	1 (9.1)

Source: Hansoh Table 3

5.3.4 Study KER050-MF-301

As described in Section 5.1.1.4, Study KER050-MF-301 is divided into 2 parts, Part 1 Dose Escalation and Part 2 Dose Expansion. In Part 1 Dose Escalation, although the dose of elritercept could be up-titrated to the RP2D once it was identified, nearly all participants remained on their starting dose over the first 24 weeks of treatment. Therefore, this initial 24-week period (also called the Base Study) provides the optimal dataset for assessing relationships between dose level and safety parameters in Study KER050-MF-301. Data from this initial 24-week period

(Base Study) are provided in [Appendix C](#). Overall, elritercept was generally well tolerated across doses as both monotherapy and in combination with ruxolitinib and there were no dose-related safety findings observed. Safety data for Study KER050-MF-301 in the remainder of Section 5.2.3 will be presented for each arm across the entire study period, irrespective of study part or starting dose level.

As described in Section 5.3.2, platelets and Hgb are not only being assessed as PD indicators of hematologic improvement, but also as safety parameters requiring dose modification if meeting certain thresholds.

5.3.4.1 Study KER050-MF-301: Extent of Exposure

In the monotherapy arm, 36 participants had a median duration of exposure of 22.9 weeks (6, 172), with 36.1% of participants having ≥ 6 months of exposure and 16.7% of participants having ≥ 12 months of exposure to elritercept.

For participants receiving combination therapy, 58 participants had a median duration of exposure of 39.3 weeks (5, 134), with 67.2% of participants having ≥ 6 months of exposure and 36.2% of participants having ≥ 12 months of exposure to elritercept.

5.3.4.2 Study KER050-MF-301: AEs

5.3.4.2.1 Study KER050-MF-301: TEAEs

Study KER050-MF-301: Overview of TEAEs: Monotherapy

Overall, 35 (97.2%) participants experienced ≥ 1 TEAE. No apparent dose-dependent TEAEs were observed for doses up to 4.5 mg/kg, as shown in [Appendix C](#). Treatment-related TEAEs of any grade and TESAEs were reported by 14 (38.9%) participants each. TEAEs leading to treatment discontinuation were reported by 10 (27.8%) participants. Fatal TEAEs were reported by 5 (13.9%) participants; these fatal events were assessed as not related to study treatment by both the treating Investigator and the Sponsor.

An overview of TEAEs reported for monotherapy is presented in [Table 5.m](#).

Table 5.m Overview of TEAEs in Monotherapy (Safety Population; Study KER050-MF-301)

	Elritercept Monotherapy (N=36) n (%)
Any TEAE	35 (97.2)
Any Treatment-Related TEAE	14 (38.9)
Any DLT	2 (5.6)
Any TESAE	14 (38.9)
Any Treatment-Related TESAE	1 (2.8)
Any TEAE Leading to Death	5 (13.9)

Table 5.m Overview of TEAEs in Monotherapy (Safety Population; Study KER050-MF-301)

	Elritercept Monotherapy (N=36) n (%)
Any TEAE Leading to Treatment Discontinuation	10 (27.8)
Any Grade ≥ 3 TEAE	22 (61.1)
Any Treatment-Related Grade ≥ 3 TEAE	4 (11.1)

Source: Table 14.3.1.1.LT

Safety Population included all participants who received ≥ 1 dose of study drug (elritercept with or without Ruxolitinib).

A TEAE was defined as an AE that commences on or after the first dose of elritercept and within 60 days after the last dose of elritercept, or analysis cutoff date, whichever was earlier in LTS.

LTS study was defined as the entire study period counting from C1D1.

Treatment-related AEs were defined as any AE with relationship to study drug as possible, probably, or highly probable. If relationship to study drug was missing, the relationship was considered as related.

Study KER050-MF-301: Overview of TEAEs: Combination Therapy

Overall, 56 (96.6%) participants experienced ≥ 1 TEAE. No apparent dose-dependent TEAEs were observed for doses up to 4.5 mg/kg of elritercept in combination with ruxolitinib, as shown in [Appendix C](#). No DLTs were reported. Elritercept-related TEAEs of any grade and Ruxolitinib-related TEAEs of any grade were reported by 23 (39.7%) participants each. TESAEs were reported by 22 (37.9%) participants. TEAEs leading to discontinuation of elritercept were reported by 4 (6.9%) participants, and TEAEs leading to discontinuation of ruxolitinib were reported by 3 (5.2%) participants. Fatal TEAEs were reported by 3 (5.2%) participants and were assessed as not related to study treatment by both the treating investigator and the sponsor.

An overview of TEAEs for combination therapy is presented in [Table 5.n](#).

Table 5.n Overview of TEAEs in Combination Therapy (Safety Population; Study KER050-MF-301)

	Elritercept + Ruxolitinib (N=58) n (%)
Any TEAE	56 (96.6)
Any Treatment-Related TEAE	30 (51.7)
Any Elritercept-Related TEAE	23 (39.7)
Any Ruxolitinib-Related TEAE	23 (39.7)
Any DLT	0
Any TESAE	22 (37.9)
Any Elritercept-Related TESAE	2 (3.4)
Any Ruxolitinib-Related TESAE	3 (5.2)

Table 5.n Overview of TEAEs in Combination Therapy (Safety Population; Study KER050-MF-301)

	Elritercept + Ruxolitinib (N=58) n (%)
Any TEAE Leading to Death	3 (5.2)
Any TEAE Leading to Elritercept Discontinuation	4 (6.9)
Any TEAE Leading to Ruxolitinib Discontinuation	3 (5.2)
Any TEAE Leading to Ruxolitinib Dose Increase	3 (5.2)
Any Grade ≥ 3 TEAE	36 (62.1)
Any Elritercept-Related Grade ≥ 3 TEAE	8 (13.8)
Any Ruxolitinib-Related Grade ≥ 3 TEAE	7 (12.1)

Source: Table 14.3.1.1.LT

Safety Population included all participants who received ≥ 1 dose of study drug (elritercept with or without Ruxolitinib).

A TEAE was defined as an AE that commences on or after the first dose of elritercept and within 60 days after the last dose of elritercept, or analysis cutoff date, whichever was earlier in LTS.

LTS study was defined as the entire study period counting from C1D1.

Treatment-related AEs were defined as any AE with relationship to study drug as possible, probably, or highly probable. If relationship to study drug was missing, the relationship was considered as related.

Study KER050-MF-301: TEAEs: Monotherapy

One participant in the 1.5 mg/kg dose cohort experienced a DLT of haemoglobin increased (from 10.2 g/dL at C1D1 to 12.1 g/dL at Cycle 2 Day 1), meeting protocol criteria for dose reduction at the end of Cycle 1. Per-protocol dose reduction did not occur (major protocol deviation), and the participant continued dosing. There was no toxicity associated with this event, and the maximum Hgb reached in the subsequent weeks was within normal limits. This event was not reported as a DLT by the treating Investigator and there was no associated toxicity, but it was considered as a DLT by the SRC based on protocol-defined DLT criteria. Another participant in the 4.5 mg/kg dose cohort experienced a DLT of Grade 2 diarrhoea on Study Day 226 for which treatment was discontinued. The event resolved ~ 1 week later and was assessed as not related by the investigator, but was considered by the SRC to be significant enough to be categorized as a DLT.

The most frequently reported ($\geq 15\%$ participants) TEAEs by MedDRA PT in participants receiving monotherapy included thrombocytopenia (11 participants, 30.6%), diarrhoea (9 participants, 25.0%), and pyrexia (8 participants, 22.2%).

TEAEs reported in $\geq 10\%$ of participants receiving monotherapy are provided in [Table 5.o](#).

Table 5.o TEAEs Reported in $\geq 10\%$ Participants by Preferred Term in Monotherapy (Safety Population; Study KER050-MF-301)

Preferred Term	Elritercept Monotherapy (N=36) n (%)
Participants with at least 1 TEAE	35 (97.2)
Thrombocytopenia	11 (30.6)
Diarrhoea	9 (25.0)
Pyrexia	8 (22.2)
Asthenia	5 (13.9)
Headache	5 (13.9)
Hypertension	5 (13.9)
Arthralgia	4 (11.1)
Cough	4 (11.1)
Dizziness	4 (11.1)
Fatigue	4 (11.1)
Neutropenia	4 (11.1)
Pneumonia	4 (11.1)

Source: Table 14.3.1.5.LT

AEs were coded with MedDRA Dictionary version 24.0.

Study KER050-MF-301: TEAEs Combination Therapy

The most frequently reported ($\geq 15\%$ participants) TEAEs by MedDRA PT in participants receiving combination therapy included diarrhea (15 participants, 25.9%), anaemia (10 participants, 17.2%), and thrombocytopenia (9 participants, 15.5 %). The majority of TEAEs were reported by 1 (1.7%) participant each.

TEAEs reported in $\geq 10\%$ participants receiving combination therapy are provided in [Table 5.p](#).

Table 5.p TEAEs Reported in $\geq 10\%$ Participants by Preferred Term in Combination Therapy (Safety Population; Study KER050-MF-301)

Preferred Term	Elritercept + Ruxolitinib (N=58) n (%)
Participants with at least 1 TEAE	56 (96.6)
Diarrhoea	15 (25.9)
Anaemia	10 (17.2)
Fatigue	8 (13.8)
Thrombocytopenia	9 (15.5)
Alanine aminotransferase increased	8 (13.8)
Cough	8 (13.8)

Table 5.p TEAEs Reported in $\geq 10\%$ Participants by Preferred Term in Combination Therapy (Safety Population; Study KER050-MF-301)

Preferred Term	Elritercept + Ruxolitinib (N=58) n (%)
Epistaxis	8 (13.8)
Constipation	7 (12.1)
Hypertension	7 (12.1)
Nausea	7 (12.1)
Urinary tract infection	7 (12.1)
Aspartate aminotransferase increased	6 (10.3)
Asthenia	6 (10.3)
Dyspnoea	6 (10.3)
Oedema peripheral	6 (10.3)

Source: Table 14.3.1.5.LT

AEs were coded with MedDRA Dictionary version 24.0.

5.3.4.2.2 Study KER050-MF-301: Treatment-Related TEAEs

Study KER050-MF-301: Treatment-related TEAEs: Monotherapy

TEAEs that were assessed as related to elritercept by the treating Investigator were reported in a total of 8 participants (34.8%) receiving monotherapy. None of these treatment-related TEAEs were reported in more than one participant. Treatment-related TEAEs included abdominal pain upper, ageusia, arthralgia, joint swelling, bone pain, cardiac failure, decreased appetite, weight decreased, dizziness, vertigo, hypertension, mucosal induration, injection site erythema, injection site pruritus, and injection site reaction.

ISRs were reported in total of 3 (13.0%) participants, and all were Grade 1 in severity, localized and resolved without any dose modifications.

Study KER050-MF-301: Treatment-related TEAEs: Combination therapy

TEAEs that were assessed as related to elritercept by the treating Investigator, were reported in a total of 11 participants (35.5%) receiving combination therapy. Treatment-related TEAEs by MedDRA PT reported by ≥ 2 participants included hypertension (2 participants, 6.5%). TEAEs that were assessed as related to ruxolitinib by the treating Investigator were reported in a total of 9 (29.0%) participants receiving combination therapy. None of these ruxolitinib-related TEAEs were reported in more than one participant. TEAEs that were assessed as related to both elritercept and ruxolitinib by the treating Investigator, were reported in a total of 5 participants and included constipation, confusional state, bone pain, hypertension, hyperferritinaemia, bradycardia and electrocardiogram QT prolonged.

5.3.4.2.3 Study KER050-MF-301: TEAEs of Grade ≥ 3

Study KER050-MF-301: $\geq$ Grade 3: Monotherapy

Grade ≥ 3 TEAEs were reported in a total of 22 (61.1%) participants receiving monotherapy. Grade ≥ 3 TEAEs reported by ≥ 2 participants by MedDRA PT included thrombocytopenia (9 participants, 25.0%), and anaemia, neutropenia, pneumonia (3 participants, 8.3%), and asthenia and pyrexia, (2 participants, 5.6%). Most Grade ≥ 3 TEAEs were reported by 1 (2.8%) participant each.

Elritercept-related Grade ≥ 3 TEAEs were reported by 4 (11.1%) participants receiving monotherapy. These elritercept-related Grade ≥ 3 TEAEs included thrombocytopenia (2 participants, 5.6%) and fall (1 participant, 2.8%), and 1 TEAE which is uncoded as of the DCO date.

Study KER050-MF-301: $\geq$ Grade 3: Combination Therapy

Grade ≥ 3 TEAEs were reported in a total of 36 participants (62.1%) receiving combination therapy. TEAEs Grade ≥ 3 reported by ≥ 2 participants by MedDRA PT included anaemia thrombocytopenia and anaemia (7 participants, 12.1%), ALT increased and hypertension (3 participants, 5.2%), and neutropenia, diverticulitis, pneumonia, AST increased, haemoglobin decreased, platelet count decreased, asthenia and fatigue (2 participants, 3.4% each).

Elritercept-related Grade ≥ 3 TEAEs were reported by 8 (13.8%) participants receiving combination therapy. These elritercept-related Grade ≥ 3 TEAEs included anaemia and thrombocytopenia (2 participants, 3.4%), and ALT increased, platelet count decreased, hepatic encephalopathy, hypertension (1 participant, 1.1% each), and 2 TEAEs which were uncoded as of the DCO date.

Ruxolitinib-related Grade ≥ 3 TEAEs were reported by 7 (12.1%) participants receiving combination. These ruxolitinib-related Grade ≥ 3 TEAEs included anaemia and platelet count decreased (2 participants, 3.4%) and thrombocytopenia, ALT increased, AST increased, gamma-glutamyltransferase increased, and rectal haemorrhage (1 participant, 1.7%), and 1 TEAE which is uncoded as of the DCO date.

The majority of Grade ≥ 3 TEAEs observed in combination therapy were reported by 1 (1.7%) participant each.

5.3.4.2.4 Study KER050-MF-301 TESAEs

Study KER050-MF-301: TESAEs: Monotherapy

TESAEs were reported in a total of 14 (38.9%) participants receiving monotherapy. TESAEs reported by ≥ 2 participants by MedDRA PT included pneumonia (3 participants; 8.3% each and pyrexia (2 participants; 5.6%). Most TESAEs were reported by 1 (2.8%) participant each.

One participant experienced a treatment-related TESAEs of Grade 3 fall.

Study KER050-MF-301: TESAEs: Combination therapy

TESAEs were reported in a total of 22 (37.9%) participants receiving combination therapy. pneumonia and vomiting were reported for 2 (3.4%) participants each. Most TESAEs were reported by 1 (1.7%) participant each.

Two (3.4%) elritercept-related TESAEs were reported (Grade 3 fall; Grade 4 anaemia). A ruxolitinib-related TESA (external ear neoplasm malignant) was reported in 1 (3.2%) participant and was assessed as related to ruxolitinib by the Sponsor as non-melanoma skin cancers, including basal cell, squamous cell, and Merkel cell carcinoma, have been reported in patients treated with ruxolitinib in ruxolitinib clinical studies.

5.3.4.2.5 Study KER050-MF-301: TEAEs leading to Death

Study KER050-MF-301: TEAEs leading to Death Monotherapy

There were no treatment-related deaths; a total of 5 (13.9%) treatment-emergent deaths were reported as of the DCO date. Fatal TEAEs leading to death included pneumonia aspiration, leukemia, multiple organ dysfunction syndrome, pneumonia, and septic shock (1 [2.8%] participant each).

Study KER050-MF-301: Deaths: Combination therapy

There were no treatment-related deaths; a total of 3 deaths, all on-treatment, were reported as of the DCO date. These deaths in 3 (5.2%) participants were due to fatal TEAEs of cerebrovascular accident, transformation to acute myeloid leukaemia, and staphylococcal sepsis, all of which were assessed as not related to study treatment.

5.3.4.2.6 Study KER050-MF-301: TEAEs Leading to Dose Modification-Monotherapy

Study KER050-MF-301: TEAEs Leading to Dose Modification-Monotherapy

TEAEs leading to dose modification (dose interruption or dose reduction) were reported in a total of 6 (16.7%) monotherapy participants and included PTs (for 1 [2.8%] participant each) of gastroenteritis, respiratory tract infection viral, ALT increased, blood alkaline phosphatase increased, gamma glutamyl transferase increased, oropharyngeal pain, thrombocytosis, visual impairment, and joint swelling, proteinuria, and weight decreased.

Only the TEAE of weight decreased led to dose reduction in the monotherapy arm; all other dose modifications were dose interruptions.

TEAEs leading to discontinuation of elritercept were reported in a total of 10 (27.8%) participants receiving monotherapy. With the exception of splenomegaly (reported in 2 participants, 5.6%), all TEAEs leading to discontinuation were reported in one (2.8%) participant each and included AML, amyloidosis, cardiac failure, chronic obstructive pulmonary disease, diarrhoea, dizziness, fall, leukemia, and pneumonia, and septic shock. All of these TEAEs leading to discontinuation except for dizziness were assessed as not related to study

treatment by the treating Investigator. Most of these events were related to worsening of concomitant comorbid conditions.

Study KER050-MF-301: TEAEs Leading to Dose Modification-Combination Therapy

TEAEs leading to elritercept dose modification (dose interruption or dose reduction) were reported in a total of 13 (22.4%) participants receiving combination therapy. Of these, ALT increased, anaemia, and platelet count increased were reported for 2 (3.4%) participants; all others were reported for one participant each and included PTs of respiratory syncytial virus infection, soft tissue infection, urinary tract infection, AST increased, pulmonary embolism, acute myocardial infarction, cardiac disorder, transient ischemic attack, renal cyst ruptured, herpes zoster, pneumonia, platelet count decreased, gastrointestinal haemorrhage, fatigue, and delirium.

Only the TEAEs of fatigue and platelet count increased led to dose reduction in the combination arm; all other dose modifications were dose interruptions.

TEAEs leading to discontinuation of elritercept were reported in a total of 4 (6.9%) participants receiving combination therapy. All TEAEs leading to discontinuation were reported by one (3.2%) participant each and included abdominal infection, staphylococcal sepsis, transformation to AML, and cerebrovascular accident.

5.3.4.2.7 Immunologic TEAEs

Monotherapy

Of the 4 participants who had ADA-positive results, ≥ 1 TEAE was reported in all 4 (100.0%) participants. Headache, diarrhoea, hypertension, weight decreased, and anaemia were reported in 2 (50.0%) participants each; all other TEAEs were reported for 1 participant only.

Most of these events were mild to moderate in severity and nonserious. Some events, such as injection site erythema, headache, and hypertension, can be signs/symptoms of an immunologic reaction; however, there was no apparent difference in the incidence of these events between the participants testing positive and those testing negative for ADA.

Combination therapy

Of the 4 participants who had ADA-positive results, ≥ 1 TEAE was reported in all 4 (100.0%) participants. Of these TEAEs, only back pain was reported for 2 participants; all other of these TEAEs were reported for 1 participant only.

These events were nonserious. There was no apparent difference in the incidence of these events between the participants testing positive and those testing negative for ADA.

5.3.5 Safety Conclusions

Single and multiple doses of elritercept up to 4.5 mg/kg were well tolerated in the completed phase 1 Study KER-050-01 conducted in healthy postmenopausal women. There were no DLTs

observed, and the MTD was not reached. The most common TEAEs observed by MedDRA PT following elritercept administration included HgB increased, headache, hypertension, nausea, and upper respiratory tract infection. Increase in HgB and associated hypertension are consistent with the known pharmacological activity of elritercept on increasing RBC production. No TESAEs, fatal TEAEs, or TEAEs leading to treatment discontinuation were reported.

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 Study KER050-MD-201. There were no DLTs at any of the 5 dose levels evaluated (up to 5.0 mg/kg) in the Part 1 Base Study, and the MTD was not identified. As of the DCO date, the most frequently reported ($\geq 15\%$ participants) TEAEs by MedDRA PT included diarrhoea, fatigue, COVID 19, anaemia, dizziness, epistaxis, nausea, dyspnoea, constipation, fall, and oedema peripheral. TESAEs reported for ≥ 3 participants (2.8%) included anaemia, pneumonia, dyspnoea, syncope. Treatment emergent deaths occurred in 6 (5.5%) participants due to fatal TEAEs of cardiac failure, idiopathic pulmonary fibrosis, myocardial infarction, non-Hodgkin lymphoma, obesity cardiomyopathy, and sudden death, all of which were assessed as not related to study treatment. TEAEs leading to discontinuation of study treatment were reported in a total of 19 (17.4%) participants. Of these, only dyspnoea was reported for 2 (1.8%) participants.

As of the DCO date, findings from the ongoing phase 2 Study HS-20106 in participants with MDS with anemia in China were consistent with the results in the Study KER050-MD-201. Overall, 6 (54.5%) participants have experienced ≥ 1 TEAE (Table 5.1), with only influenza like illness, platelet count decreased, and white blood cell count decreased reported for ≥ 2 (18.1%) participants. No TEAEs leading to treatment discontinuation and no TESAEs have been reported.

As of the DCO date, the safety findings from the ongoing phase 2 Study KER050-MF-301 in participants with MF receiving elritercept either as monotherapy or in combination with ruxolitinib at doses of 0.75, 1.5, 3.0, and 4.5 mg/kg were consistent with the results in the other ongoing phase 2 trials, Study KER050-MD-201 and Study HS-20106-201 in participants with LR-MDS. No apparent dose-dependent TEAEs were observed for doses up to 4.5 mg/kg, both as monotherapy and in combination with ruxolitinib. One DLT of HgB increased was experienced by a participant. There was no toxicity associated with this event and the maximum Hgb reached in the subsequent weeks was within normal limits and did not impact the dose-escalation based on Bayesian optimal interval design outlined in the protocol. Another participant experienced a DLT of Grade 2 diarrhea for which treatment was discontinued. There were no other DLTs and the MTD was not reached. As with the Study KER050-MD-201, based on these observed safety findings, in addition to the PK/PD and preliminary efficacy data, the RP2D for Study KER050-MF-301 was determined as 3.75 mg/kg SC Q4W, with the option to up-titrate to 5.0 mg/kg or down-titrate to 2.5 mg/kg or 1.5 mg/kg, depending on individual participant's hematological response or safety findings, respectively.

Monotherapy

- The most frequently reported ($\geq 15\%$ participants) TEAEs by MedDRA PT included thrombocytopenia, diarrhoea, and pyrexia.

- TESAEs reported by ≥ 2 participants by MedDRA PT included pneumonia and pyrexia. Most TESAEs were reported by 1 (2.8%) participant each.
- Related Grade ≥ 3 TEAEs included thrombocytopenia and fall.
- A total of 5 (13.9%) treatment-emergent deaths were reported and were all assessed as not related to the study treatment.
- TEAEs leading to discontinuation of elritercept were reported in a total of 10 (27.8%) participants and the only related TEAE that led to discontinuation of elritercept was dizziness.

Combination therapy

- The most frequently reported ($\geq 15\%$ participants) TEAEs by MedDRA PT included diarrhoea, anaemia, and thrombocytopenia.
- TESAEs were reported in a total of 22 (37.9%). Pneumonia and vomiting were the most frequently reported TESAEs.
- Elritercept-related Grade ≥ 3 TEAEs included anaemia, thrombocytopenia, ALT increased, platelet count decreased, hepatic encephalopathy, and hypertension. Ruxolitinib-related Grade ≥ 3 TEAEs included anaemia, platelet count decreased, thrombocytopenia, ALT increased, AST increased, gamma glutamyltransferase increased, and rectal haemorrhage.
- A total of 3 (5.2%) treatment-emergent deaths were reported and were all assessed as not related to the study treatment.
- TEAEs leading to discontinuation of elritercept were reported in a total of 4 (6.9%) participants and included abdominal infection, staphylococcal sepsis, transformation to AML, and cerebrovascular accident.

Across all clinical studies, incidences of ADA positivity were low and, in most cases, have not been shown to impact exposure to elritercept. The low overall incidence and titers of ADAs in participants suggests that immunogenicity is not a substantial potential risk.

Overall, elritercept has an acceptable and manageable safety profile supporting further clinical development.

5.4 Clinical Efficacy

The phase 1 FIH KER-050-01 is the only trial completed to date. The trial was conducted in healthy participants and therefore not designed to evaluate the effects of elritercept on anemia; however, in the trial, treatment with elritercept elicited clinically relevant, dose dependent increases in PD markers of hematopoiesis. These findings support a potential clinical benefit for elritercept in treating anemia in participants with MDS and MF.

5.5 Marketing Experience

Elritercept is not marketed in any country.

6.0 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

The updates contained in this IB (Edition 8) are considered nonsubstantial because changes were not made to the RSI for expectedness of SARs for regulatory reporting purposes (Section 6.4.1), the overall benefit-risk profile for elritercept did not change (Section 6.3 and Section 6.4, respectively), and there is no new toxicology or pharmacological information.

6.1 Summary of Nonclinical Studies

Repeat-dose toxicology studies of 35-days and 3-months duration were performed with elritercept in Sprague Dawley rats and for 35-days, 3-months, and 6-months duration in NHPs.

There was no elritercept-related mortality in the studies conducted in NHPs, however, in the rat there were 2 early deaths in the 3-month study that were considered elritercept-related; 1 death was attributed to urinary bladder hemorrhage consistent with obstruction and the other was due to undetermined causes.

Changes in the kidney were considered adverse in the high-dose (50 mg/kg/dose) animals in the 3-month studies and included hemorrhage and fibrosis in the NHP and minimal-to-moderate necrosis of tubules in the papilla in the rat.

Reproductive tissue changes were considered to be pharmacologically mediated and were non-adverse with the exception of the effects on reproductive development. These included mammary gland hyperplasia, increased corpora lutea, and vaginal mucification. Reduced embryo-fetal viability was observed in a rat developmental toxicity study. In a rat fertility study, there was prolongation of the estrous cycle, though there were no direct effects on female or male fertility.

Bone and adrenal glands changes in the rat were also adverse; however, they were considered a species-specific finding. The bone changes may be related to the rapid remodeling of skeletal bone in rodents combined with the elritercept effects on hematopoiesis and bone growth. The adrenal gland changes may be attributed to the differences in the maturation of this organ in this species. Additional non-adverse changes observed in nonclinical toxicology studies include liver, bone marrow, salivary glands, and hematology and serum chemistry parameters.

6.2 Summary of Clinical Studies

Elritercept drug product (Solution for Injection) is administered SC on a weight basis at dose levels and dose frequency per trial protocols. For additional information on the administration of elritercept, please refer to the trial's Pharmacy Manual

As of the DCO date 03 Apr 2025, elritercept has been evaluated in 4 clinical trials: a phase 1 dose-escalation trial in healthy postmenopausal women (Study KER-050-01); a phase 2 open-label, ascending-dose trial in participants with MDS (Study KER050-MD-201); a phase 2 trial in participants with anemia due to LR-MDS in the territory of mainland China (Study HS

20106 20); and a phase 2 open-label, ascending-dose trial in participants with MF (Study KER050-MF-301). In addition, a phase 3 double-blind, placebo-controlled trial in participants with LR-MDS (KER 050-D301) is currently ongoing. An overview of the elritercept clinical studies is provided in [Table 5.a](#).

6.2.1 Clinical Pharmacokinetics

Elritercept is absorbed following SC administration, with a median $T_{\max}$ of approximately 4.5 to 6 days in healthy postmenopausal women, and slowly eliminated, with a mean $t_{1/2}$ of approximately 12 days. Serum elritercept exposure was dose-proportional in healthy postmenopausal women, across a dose range of 0.5 to 4.5 mg/kg. In participants with MDS, elritercept concentrations increased with increasing dose following Q4W SC administration across the dose range of 0.75 to 5.0 mg/kg. No consistent evidence of accumulation has been observed in healthy postmenopausal women, participants with MDS or MF. Incidence of ADA is low and does not appear to have any overt effects on serum elritercept exposure.

6.2.2 Clinical Pharmacodynamics

Several PD markers were assessed to understand the effects of elritercept on target signaling pathways and tissues as well as effects in stimulating hematopoiesis. In general, observed changes in PD markers were consistent with those expected following inhibition of ActRIIA ligands and supported a mechanism whereby elritercept can promote differentiation and maturation of both erythroid and megakaryocyte progenitors. Also, PD changes generally showed dose effects, however, interpretation of dose effects in Study KER050-MD-201 and KER050-MF-301 is limited by small cohort sizes and considerable heterogeneity among participants with regard to baseline disease characteristics.

After treatment with elritercept, the following key PD effects were observed:

In healthy postmenopausal women:

- Rapid, dose-dependent increases in reticulocytes, RBCs, and Hgb were observed following a single dose
- Increases in RBCs and Hgb were sustained beyond Day 42 following a single dose suggesting potential not only to stimulate release of late-stage erythroid precursors but potentially to support continued propagation of precursors along the erythroid pathway
- Decreases from baseline in FSH concentrations in elritercept-treated groups compared with increases in FSH concentrations in placebo-treated participants is indicative of activin inhibition. Increases from baseline in BSAP in healthy postmenopausal women were also observed and trended toward a dose-dependence effect, suggesting potential effects on osteoblast activity, consistent with activin inhibition.

In participants with MDS (Study KER050-MD-201):

- In the Part 1 Base Study increases in reticulocytes and Hgb were observed in all dose groups that were generally greater at higher dose levels.

- Increases in sTfR and platelets were also observed, but without any clear dose effect.
- Additional PD data pertaining to potential clinical effects in addressing anemia and aspects of MDS biology beyond anemia are presented in [5.2.2.2.1](#).

In participants with MF (Study KER050-MF-301):

- In NTD participants from Part 1 Dose Escalation, increases in markers of erythropoiesis (sTfR, reticulocytes, Hgb) were observed over the first 12 weeks of treatment that were generally greater at higher dose levels.
- Additional PD data pertaining to potential effects of elritercept on anemia, spleen volume and symptoms are presented in Section 5.5.3.

6.2.3 Clinical Summary of Safety

As of the DCO date (03 Apr 2025), safety data were available for completed phase 1 Study KER-050-01 conducted in healthy postmenopausal women treated with monotherapy elritercept or placebo (38 participants and 10 participants, respectively); participants from ongoing phase 2 Study KER050-MD-201 in participants with LR-MDS treated with monotherapy elritercept (109 participants); ongoing phase 2 Study HS-20106-201 in participants with anemia due to LR-MDS treated with monotherapy elritercept (11 participants); and ongoing phase 2 Study KER050-MF-301 in participants with MF treated with monotherapy elritercept or combination therapy with elritercept and ruxolitinib (36 participants and 58 participants, respectively).

Overall, elritercept thus far has an acceptable and manageable safety profile supporting further clinical development. Please refer to Section [5.3.5](#) for detailed safety data.

6.3 Potential Benefits

The current safety and clinical benefit data for elritercept support a positive benefit/risk profile for participants with LR-MDS and MF.

The phase 1 FIH KER-050-01 trial was conducted in healthy participants and therefore not designed to evaluate the effects of elritercept on anemia; however, in the trial, treatment with elritercept elicited clinically relevant, dose-dependent increases in PD markers of hematopoiesis. These findings support a potential clinical benefit for elritercept in treating anemia in participants with MDS and MF.

Preliminary PD and efficacy results from the ongoing KER050-MD-201 trial demonstrate potential for elritercept treatment at the recommended phase 2 dose (RP2D) to provide durable hematological benefits, including transfusion independence (TI) ≥ 24 weeks, in a broad population of patients with LR-MDS, including difficult-to-treat patients with HTB and/or non-ring sideroblasts disease (RS) ([Giagounidis et al. 2024](#)). Improvements in quality-of-life measures observed in erythroid responders support broad potential for benefit in an LR-MDS population. ([Giagounidis et al. 2024](#)). Furthermore, additional preliminary 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 contribute to increased morbidity and mortality in patients with LR-MDS ([Tan et al. 2024](#); [Valcárcel et al. 2024](#)).

Preliminary PD and efficacy results from the ongoing KER050-MF-301 trial support similar potential for durable hematological benefits in patients with MF, consistent with observations from Study KER050-MD-201. In addition, improvement in MF symptoms as measured by Total Symptom Score (MF-SAF-TSS) and reduction in spleen volume demonstrate potential for benefits beyond treatment of anemia ([Harrison et al. 2024](#)).

6.4 Emerging Safety Information

6.4.1 RSI for Assessment of Expectedness of SARs

The RSI provides a list of adverse reactions considered expected for the purposes of expedited reporting to Regulatory Authorities, that is, to determine whether certain events would be deemed a SUSAR should a SAR occur.

Elritercept monotherapy: No SARs are considered expected by the sponsor for the purposes of regulatory reporting, any SARs would therefore be considered as SUSARs.

Elritercept + Ruxolitinib combination regimen: no SARs are considered expected by the sponsor for the purpose of expedited reporting, any SARs would therefore be considered as SUSARs.

Importantly, life-threatening or fatal adverse reactions are considered unexpected by the sponsor for expedited reporting of SUSARs.

6.5 Special Warnings and Precautions for Use

Embryo-fetal toxicity: The embryo-fetal development study provided nonclinical evidence that elritercept has the potential for embryo-fetal toxicity. Participants who are currently pregnant or breastfeeding or are planning to become pregnant during elritercept clinical studies are not allowed to participate. Female participants of childbearing potential who are sexually active with members of the opposite sex will be required to use highly effective, protocol-defined contraception methods as defined in the trial protocol. Male participants who are sexually active with a female partner of childbearing potential must agree to use condoms.

Reproductive toxicity: Elritercept is expected to reduce reproductive function in both men and women as a result of its inhibition of activin. This is consistent with the findings in the repeat-dose toxicity studies where reproductive tissues (mammary glands, ovaries, vagina) were affected. Female rats had findings consistent with the estrous cycle being held in diestrus and mammary gland hyperplasia was observed in both male and female NHPs. In a rat fertility study, there was prolongation of the estrous cycle, though there were no direct effects on female or male fertility.

Hypersensitivity type reactions and immunogenicity: As with all biologics, there is potential for ADA with elritercept administration, which can be associated with increased drug clearance and hypersensitivity reactions.

ISRs were reported in a total of 21 participants treated with elritercept, comprising 3 participants in the completed Study KER-050-01; 15 participants in the ongoing Study KER050-MD-201, including 12 participants in the LTS analysis set and an additional 3 participants from the Base Study; and 3 participants in the ongoing Study KER050-MF-301. All the observed injection-site reactions were localized, mild to moderate in severity, and were managed with simple measures.

Hypertension: TEAEs of the PT hypertension have been reported in a total of 34 participants treated with elritercept, comprising 5 participants in the completed Study KER-050-01; 17 participants in the ongoing Study KER050-MD-201, including 15 participants in the LTS analysis set and an additional 2 participants from the Base Study; and 12 participants in the ongoing Study KER050-MF-301. No TEAEs of the PT hypertension have been reported for Study HS-20106-201.

Blood pressure should be monitored prior to administration of each dose of study drug in accordance with the trial protocol. Anti-hypertensive agents should be used to manage new-onset hypertension or exacerbations of preexisting hypertension.

6.6 Special Populations

To date, elritercept has not been studied in any special populations.

6.7 Contraindications

Elritercept should not be administered to individuals with known hypersensitivity to any component of the elritercept Solution for Injection.

Refer to the elritercept clinical trial protocols for specific trial exclusion criteria.

6.8 Drug Interactions and Other Forms of Interactions

The current understanding of elritercept mechanism of action does not indicate its interference with absorption and/or clearance of other drugs or expression or activity of drug metabolizing enzymes, as outlined by EMA and FDA guidance (EMA. (2018). *Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins*.; FDA. (2023). *Guidance for Industry: Drug-Drug Interaction Assessment for Therapeutic Proteins*. US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). As a consequence, the risk of clinically relevant drug-drug interaction is considered to be low.

6.9 Pregnancy and Lactation

There are no available clinical data on the use of elritercept in pregnant or breastfeeding women; however, results from a developmental toxicity animal study indicate the potential for

embryo-fetal toxicity. Participants who are currently pregnant, breastfeeding, or are planning to become pregnant during elritercept clinical studies are not allowed to participate.

Pregnancy testing is required for female participants of childbearing potential before starting study treatment and while receiving study treatment as outlined in the trial protocol. Should a participant become pregnant during the treatment period, elritercept should be discontinued immediately. Pregnancies and suspected pregnancies occurring while a participant is receiving study drug, or within 60 days of the participant's last dose of study drug, should be reported as outlined in the trial protocol. Contraception requirements for trial participants with childbearing potential are outlined in the trial protocols.

No formal studies have been performed to assess the potential for transfer of elritercept or its metabolites into human breast milk, the effects on the breastfed infant, or the effects on milk production; however, because it is known that many medicinal products, including antibodies, can be secreted into human breast milk, risk to newborns/infants cannot be excluded. Women should not breastfeed during treatment.

6.10 Overdose

Should an elritercept overdose (as defined in the protocol) occur, symptomatic management is recommended. Supportive care, symptomatic treatment, and vigilant clinical monitoring would be appropriate in these cases.

6.11 Drug Abuse and Dependence

To date, there is no evidence of drug abuse or dependence with elritercept.

6.12 Pharmaceutical Particulars

Section 3.0 contains further information about the physical, chemical, and pharmaceutical properties of Elritercept.

7.0 REFERENCES

- 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.
- Barbui, T., Thiele, J., Gisslinger, H., Kvasnicka, H. M., Vannucchi, A. M., Guglielmelli, P., et al. 2018. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. *Blood Cancer J*, 8(2), 15.
- 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.
- Bewersdorf, J. P. and Zeidan, A. M. 2019. Transforming growth factor (TGF)- β pathway as a therapeutic target in lower risk myelodysplastic syndromes. *Leukemia*, 33(6), 1303-12.
- Blank, U. and Karlsson, S. 2011. The role of Smad signaling in hematopoiesis and translational hematology. *Leukemia*, 25(9), 1379-88.

- Blum, S. and Malcovati, L. 2021. EHA Endorsement of the European Guidelines for Myelodysplastic Syndromes, MDS-RIGHT. *Hemasphere*, 5(9), e631.
- Brenet, F., Kermani, P., Spektor, R., Rafii, S. and Scandura, J. M. 2013. TGF β restores hematopoietic homeostasis after myelosuppressive chemotherapy. *J Exp Med*, 210(3), 623-39.
- Brenet, F. and Scandura, J. M. 2015. Cutting the brakes on hematopoietic regeneration by blocking TGF β to limit chemotherapy-induced myelosuppression. *Mol Cell Oncol*, 2(3), e978703.
- Cervantes, F., Dupriez, B., Pereira, A., Passamonti, F., Reilly, J. T., Morra, E., et al. 2009. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood*, 113(13), 2895-901.
- Chanut, F., Kimbrough, C., Hailey, R., Berridge, B., Hughes-Earle, A., Davies, R., et al. 2013. Spontaneous cardiomyopathy in young Sprague-Dawley rats: evaluation of biological and environmental variability. *Toxicol Pathol*, 41(8), 1126-36.
- Dayyani, F., Conley, A. P., Strom, S. S., Stevenson, W., Cortes, J. E., Borthakur, G., et al. 2010. Cause of death in patients with lower-risk myelodysplastic syndrome. *Cancer*, 116(9), 2174-9.
- 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.
- Fuller, K., Bayley, K. E. and Chambers, T. J. 2000. Activin A is an essential cofactor for osteoclast induction. *Biochem Biophys Res Commun*, 268(1), 2-7.
- Gangat, N., Caramazza, D., Vaidya, R., George, G., Begna, K., Schwager, S., et al. 2011. DIPSS plus: A refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J. Clin. Oncol*, 29(4), 392-7.
- Gangat, N. and Tefferi, A. 2020. Myelofibrosis biology and contemporary management. *Br J Haematol*, 191(2), 152-70.
- 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.
- Giagounidis, A. and Haase, S. 2020. Where does morphology fit in myelodysplastic syndrome diagnosis in the era of molecular testing? *Hematol Oncol Clin North Am*, 34(2), 321-31.
- 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.
- Harrison, C., Chee, L. C. Y., Devos, T., Fox, M. L., Iurlo, A., Palandri, F., et al. 2024. Hematological improvement and other clinical benefits of elritercept as monotherapy and in combination with ruxolitinib in participants with myelofibrosis from the ongoing phase 2 Restore trial. *Blood*, 144(Supplement 1), 997-8.

- Hinge, A. and Filippi, M. D. 2016. Deconstructing the complexity of TGF β signaling in hematopoietic stem cells: Quiescence and beyond. *Curr Stem Cell Rep*, 2(4), 388-97.
- Ikenoue, T., Jingushi, S., Urabe, K., Okazaki, K. and Iwamoto, Y. 1999. Inhibitory effects of activin-A on osteoblast differentiation during cultures of fetal rat calvarial cells. *J Cell Biochem*, 75(2), 206-14.
- Kasprzak, A., Kaivers, J., Nachtkamp, K., Haas, R., Kobbe, G., Gattermann, N., et al. 2021. Guidelines for myelodysplastic syndromes: Converting evidence into action? *Int J Environ Res Public Health*, 18(14), 7629.
- Khoury, J. D., Solary, E., Abla, 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.
- Kuykendall, A. T., Talati, C., Padron, E., Sweet, K., Sallman, D., List, A. F., et al. 2019. Genetically inspired prognostic scoring system (GIPSS) outperforms dynamic international prognostic scoring system (DIPSS) in myelofibrosis patients. *Am J Hematol*, 94(1), 87-92.
- Li, H., Hu, F., Gale, R. P., Sekeres, M. A. and Liang, Y. 2022. Myelodysplastic syndromes. *Nat Rev Dis Primers*, 8(1), 74.
- Lodberg, A. 2021. Principles of the activin receptor signaling pathway and its inhibition. *Cytokine Growth Factor Rev*, 60, 1-17.
- Massagué, J., Seoane, J. and Wotton, D. 2005. Smad transcription factors. *Genes Dev*, 19(23), 2783-810.
- Menssen, A. J. and Walter, M. J. 2020. Genetics of progression from MDS to secondary leukemia. *Blood*, 136(1), 50-60.
- Mies, A., Bulycheva, E., Rogulj, I. M., Hofbauer, L. C. and Platzbecker, U. 2016. Alterations within the osteo-hematopoietic niche in MDS and their therapeutic implications. *Curr Pharm Des*, 22(16), 2323-32.
- Moulard, O., Mehta, J., Fryzek, J., Olivares, R., Iqbal, U. and Mesa, R. A. 2014. Epidemiology of myelofibrosis, essential thrombocythemia, and polycythemia vera in the European Union. *Eur. J. Haematol*, 92(4), 289-97.
- Ning, J., Zhao, Y., Ye, Y. and Yu, J. 2019. Opposing roles and potential antagonistic mechanism between TGF- β and BMP pathways: Implications for cancer progression. *EBioMedicine*, 41, 702-10.
- 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.
- Pearsall, R. S., Canalis, E., Cornwall-Brady, M., Underwood, K. W., Haigis, B., Ucran, J., et al. 2008. A soluble activin type IIA receptor induces bone formation and improves skeletal integrity. *Proc Natl Acad Sci U S A*, 105(19), 7082-7.
- Phillips, D. J., de Kretser, D. M. and Hedger, M. P. 2009. Activin and related proteins in inflammation: not just interested bystanders. *Cytokine Growth Factor Rev*, 20(2), 153-64.
- Portale, F., Cricrì, G., Bresolin, S., Lupi, M., Gaspari, S., Silvestri, D., et al. 2019. ActivinA: a new leukemia-promoting factor conferring migratory advantage to B-cell precursor-acute lymphoblastic leukemic cells. *Haematologica*, 104(3), 533-45.

- Raaijmakers, M. H. 2012. Myelodysplastic syndromes: revisiting the role of the bone marrow microenvironment in disease pathogenesis. *Int J Hematol*, 95(1), 17-25.
- Rambaldi, B., Diral, E., Donsante, S., Di Marzo, N., Mottadelli, F., Cardinale, L., et al. 2021. Heterogeneity of the bone marrow niche in patients with myeloproliferative neoplasms: ActivinA secretion by mesenchymal stromal cells correlates with the degree of marrow fibrosis. *Ann Hematol*, 100(1), 105-16.
- Roh, J. D., Hobson, R., Chaudhari, V., Quintero, P., Yeri, A., Benson, M., et al. 2019. Activin type II receptor signaling in cardiac aging and heart failure. *Sci Transl Med*, 11(482).
- Ruiz, S., Zhao, H., Chandakkar, P., Chatterjee, P. K., Papoin, J., Blanc, L., et al. 2016. A mouse model of hereditary hemorrhagic telangiectasia generated by transmammary-delivered immunoblocking of BMP9 and BMP10. *Sci Rep*, 5, 37366.
- Sako, D., Grinberg, A. V., Liu, J., Davies, M. V., Castonguay, R., Maniatis, S., et al. 2010. Characterization of the ligand binding functionality of the extracellular domain of activin receptor type IIb. *J Biol Chem*, 285(27), 21037-48.
- Smith, R. E., Chelmowski, M. K. and Szabo, E. J. 1990. Myelofibrosis: a review of clinical and pathologic features and treatment. *Crit Rev Oncol Hematol*, 10(4), 305-14.
- Söderberg, S. S., Karlsson, G. and Karlsson, S. 2009. Complex and context dependent regulation of hematopoiesis by TGF-beta superfamily signaling. *Ann N Y Acad Sci*, 1176, 55-69.
- Suragani, R. N., Cadena, S. M., Cawley, S. M., Sako, D., Mitchell, D., Li, R., et al. 2014. Transforming growth factor- β superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. *Nat Med*, 20(4), 408-14.
- Tan, S., Chee, L., Ross, D., Cluzeau, T., Giagounidis, A., Valcárcel, D., et al. 2024. 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*. Madrid, Spain.
- Tefferi, A. 2021. Primary myelofibrosis: 2021 update on diagnosis, risk-stratification and management. *Am J Hematol*, 96(1), 145-62.
- Tefferi, A., Guglielmelli, P., Nicolosi, M., Mannelli, F., Mudireddy, M., Bartalucci, N., et al. 2018. GIPSS: genetically inspired prognostic scoring system for primary myelofibrosis. *Leukemia*, 32(7), 1631-42.
- Terpos, E., Kastritis, E., Christoulas, D., Gkatzamanidou, M., Eleutherakis-Papaiakovou, E., Kanellias, N., et al. 2012. Circulating activin-A is elevated in patients with advanced multiple myeloma and correlates with extensive bone involvement and inferior survival; no alterations post-lenalidomide and dexamethasone therapy. *Ann Oncol*, 23(10), 2681-6.
- Valcárcel, D., Giagounidis, A., Chee, L., Ross, D., Bernal, T., Tan, S., et al. 2024. 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*. Madrid, Spain.
- 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.
- Weidner, H., Rauner, M., Trautmann, F., Schmitt, J., Balaian, E., Mies, A., et al. 2017. Myelodysplastic syndromes and bone loss in mice and men. *Leukemia*, 31(4), 1003-7.

- Wijayarathna, R. and de Kretser, D. M. 2016. Activins in reproductive biology and beyond. *Hum Reprod Update*, 22(3), 342-57.
- 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.
- Zingariello, M., Martelli, F., Ciaffoni, F., Masiello, F., Ghinassi, B., D'Amore, E., et al. 2013. Characterization of the TGF- β 1 signaling abnormalities in the Gata1low mouse model of myelofibrosis. *Blood*, 121(17), 3345-63.

Appendix A SUMMARY OF TOXICOKINETIC DATA FROM COMPLETED TOXICOLOGY STUDIES

Table A1 Summary of Nonclinical Primary Toxicokinetic Studies of Elritercept in Rats

Study	Day	Dose (mg/kg)	C _{max} (ng/mL)	T _{max} (hr)	T _{last} (hr)	AUC _{0-168hr} (hr*ng/mL)	AUC _{last} (hr*ng/mL)	R _{AUC} (RATIO)
35-day Rat Toxicity (Study 2697-005)	1	3	17,800	48	168	2,210,000	2,210,000	NA
		10	61,300	72	168	7,270,000	7,270,000	NA
		50	236,000	48	168	28,700,000	28,700,000	NA
	29 ^a	3	20,500	48	504	2,020,000	3,130,000	0.915
		10	18,500	48	504	2,140,000	2,960,000	0.295
		50	106,000	48	504	9,960,000	13,900,000	0.347
3-month Rat Toxicity (Study 2849-002)	1	3	41,800	120 ^b	168	4,570,000	NA	NA
		10	120,000	144 ^b	168	12,700,000	NA	NA
		50	472,000	120 ^b	168	52,600,000	NA	NA
	85 ^a	3	5,880	1	168	765,000	NA	0.167
		10	42,300	24	168	5,610,000	NA	0.44
		50	282,000	24	168	42,400,000	NA	0.806
Rat Enhanced pEFD (Study 20344221)	6	3	20,600	72	168	2,420,000	2,420,000	NA
		10	52,800	36	168	6,920,000	6,920,000	NA
		50	226,000	48	168	24,600,000	24,600,000	NA
	13	3	27,800	36	168	2,030,000	2,030,000	0.849
		10	56,100	48	168	4,510,000	4,510,000	0.673
		50	151,000	24	168	10,300,000	10,100,000	0.403
Rat Fertility (Study 20344225) ^c	1	3	10,900	120	168	1,240,000	1,240,000	NA
		10	26,000	120	168	2,870,000	2,870,000	NA
		50	84,300	120	168	9,340,000	9,340,000	NA
	15	3	6,010	24	168	309,000	309,000	0.256
		10	8,680	36	144	573,000	560,000	0.193
		50	50,000	24	168	2,580,000	2,580,000	0.281

Dosing schedule in Study 2697-005 and Study 20344221 is once weekly; and dosing schedule in Study 2849-002 and Study 20344225 is twice weekly.

^a Values affected by immunogenicity.

^b T_{max} values >72 hours are following the second weekly dose.

^c Values represent both male and female values combined.

Table A2 Summary of Nonclinical Primary Toxicokinetic Studies of Elritercept in Rats

Study	Day	Female		Male	Female:Male (RATIO)
		Dose (mg/kg)	AUC _{0-168hr} (hr*ng/mL)	AUC _{0-168hr} (hr*ng/mL)	
35-day Rat Toxicity (Study 2697-005)	1	3	2,410,000	2,000,000	1.21
		10	8,120,000	6,420,000	1.26
		50	30,200,000	27,100,000	1.11
	29 ^a	3	1,630,000	2,410,000	0.68
		10	385,000	3,460,000	0.11
		50	14,200,000	5,660,000	2.51
3-month Rat Toxicity (Study 2849-002)	1	3	4,900,000	4,240,000	1.15
		10	14,300,000	11,200,000	1.28
		50	61,800,000	43,400,000	1.43
	85 ^a	3	NA ^b	1,530,000	NA
		10	2,750,000	8,470,000	0.324
		50	54,200,000	30,600,000	1.77
Rat Fertility (Study 20344225)	1	3	1,310,000	1,170,000	1.1
		10	2,740,000	3,010,000	0.9
		50	10,000,000	8,640,000	1.2
	15	3	192,000	425,000	0.5
		10	456,000	691,000	0.6
		50	2,270,000	2,900,000	0.8

^a Values affected by immunogenicity.

^b All serum concentrations were below the limit of quantitation.

Table A3 Summary of Nonclinical Primary Toxicokinetic Studies of Elritercept in Cynomolgus Monkeys

Study	Day	Dose (mg/kg)	C _{max} (ng/mL)	T _{max} (hr)	T _{last} (hr)	AUC _{0-168hr} (hr*ng/mL)	AUC _{0-336hr} (hr*ng/mL)	R _{AUC} (RATIO)
35-day Cynomolgus Monkey Toxicity (Study 2697-006)	1	3	32,600	48	336	4,160,000	6,370,000	NA
		10	113,000	48	336	14,200,000	22,100,000	NA
		50	552,000	48	336	69,800,000	112,000,000	NA
	29	3	38,300	48	168	5,110,000	8,220,000	1.24
		10	141,000	48	168	18,600,000	28,300,000	1.32
		50	718,000	48	168	90,500,000	132,000,000	1.3
3-month Cynomolgus Monkey Toxicity (Study 2849-001)	1	3	30,000	48	336	4,090,000	6,250,000	NA
		10	108,000	48	336	14,200,000	22,200,000	NA
		50	488,000	48	336	63,400,000	101,000,000	NA
	85	3	39,700	48	168	5,460,000	9,130,000	1.34
		10	147,000	48	168	19,500,000	28,000,000	1.4
		50	893,000	48	168	111,000,000	163,000,000	1.77
6-month Cynomolgus Monkey Toxicity (Study 2849-007)	1	3	19,100	NA	336	2,380,000	3,450,000	NA
		10	61,100	24	336	7,790,000	11,600,000	NA
		30	189,000	24	336	23,200,000	35,200,000	NA
	169	3	23,700	48	168	2,980,000	3,730,000	1.27
		10	81,600	NA	168	10,500,000	12,500,000	1.36
		30	315,000	24	168	37,000,000	48,600,000	1.62

Table A4 Summary of Nonclinical Primary Toxicokinetic Studies of Elritercept in Cynomolgus Monkeys

Study	Day	Dose (mg/kg)	Female	Male	Female:Male (RATIO)
			AUC _{0-168hr} (hr*ng/mL)	AUC _{0-168hr} (hr*ng/mL)	
35-day Cynomolgus Monkey Toxicity (Study 2697-006)	1	3	4,190,000	4,130,000	1.02
		10	14,800,000	13,700,000	1.08
		50	69,000,000	70,700,000	0.975
	29	3	5,510,000	4,700,000	1.17
		10	17,800,000	19,400,000	0.914
		50	79,900,000	101,000,000	0.79
3-month Cynomolgus Monkey Toxicity (Study 2849-001)	1	3	3,970,000	4,200,000	0.946
		10	13,100,000	15,300,000	0.853
		50	61,500,000	65,200,000	0.943
	85	3	5,860,000	5,070,000	1.16
		10	17,800,000	21,100,000	0.844
		50	108,000,000	115,000,000	0.943
6-month Cynomolgus Monkey Toxicity (Study 2849-007)	1	3	2,250,000	2,500,000	0.898
		10	7,580,000	7,990,000	0.949
		30	23,700,000	22,700,000	1.04
	169	3	3,060,000	2,880,000	1.06
		10	10,600,000	10,400,000	1.02
		30	36,900,000	37,200,000	0.992

Table A5 Summary of Nonclinical Secondary Toxicokinetic Studies of Elritercept in Rats

Study	Day	Dose (mg/kg)	CL/F ^a (mL/hr/kg)	V _z /F ^a (mL/kg)	t _{1/2} (hr)
35-day Rat Toxicity (Study 2697-005)	1	3	NA ^b	NA ^b	127 ^c
		10	NA ^b	NA ^b	NA ^b
		50	NA ^b	NA ^b	104
	29	3	0.957	NA ^b	NA ^b
		10	3.38	NA ^b	NA ^b
		50	3.60	532	102
3-month Rat Toxicity (Study 2849-002)	1	3	NA ^b	NA ^b	NA ^b
		10	NA ^b	NA ^b	NA ^b
		50	NA ^b	NA ^b	NA ^b
	85	3	NA ^b	NA ^b	NA ^b
		10	NA ^b	NA ^b	NA ^b
		50	NA ^b	NA ^b	NA ^b
Rat Fertility (Study 20344225)	1	3	NA ^b	NA ^b	NA ^b
		10	NA ^b	NA ^b	NA ^b
		50	NA ^b	NA ^b	NA ^b
		3	NA ^b	NA ^b	NA ^b
	15	10	13.8	722	36.2
		50	18.8	741	29.9

^a Secondary parameters on Day 29 were calculated using steady state formulas.

^b Secondary parameters not reported due to insufficient data.

^c t_{1/2} value determined using less than 3 half-lives of data (t_{1/2} >56 hours).

Table A6 Summary of Nonclinical Secondary Toxicokinetic Studies of Elritercept in Cynomolgus Monkeys

Study	Day	Dose	CL/F ^a	V _z /F ^a	t _½
		(mg/kg)	(mL/hr/kg)	(mL/kg)	(hr)
35-day Cynomolgus Monkey	1	3	0.387	74.4	151
		10	0.369	74.6	169
		50	0.400	80.8	164
Toxicity (Study 2697- 006)	29	3	0.522	72.0	129
		10	0.461	78.6	138
		50	0.48	62.3	129
3-month Cynomolgus Monkey	1	3	0.394	76.6	102
		10	0.378	80.3	NA
		50	0.448	90.8	NA
Toxicity (Study 2849- 001)	85	3	0.319	62.9	NA
		10	0.341	75.5	NA
		50	0.297	92.5	99.3
6-month Cynomolgus Monkey	1	3	0.691	124	127
		10	0.731	125	121
		30	0.692	139	152
Toxicity (Study 2849- 007)	169	3	0.913	98.6	100
		10	0.658	NA	110
		30	0.466	NA	149

^a Secondary parameters on Day 85 were calculated using steady state formulas.

Appendix B SUMMARY OF NONCLINICAL PHARMACOLOGY STUDIES OF ELRITERCEPT/RKER-050

Table A7 Summary of Nonclinical Pharmacology Studies of Elritercept/RKER-050

Study Number	Study Description	Species/Strain/Sex (N)	Drug	RKER-050/ Elritercept Source	Dose, Route, Duration	Results
KTR-03	Analysis of elritercept binding to TGF- β superfamily ligands by surface plasmon resonance	NA	elritercept	Stable CHO cell line	50-250 resonance units of elritercept captured on chip	Activin A, activin B, GDF8, and GDF11 are ligands with tightest binding affinities (9-32 pM).
KTR-02	Elritercept inhibition of SMAD signaling in luciferase reporter assays	NA	elritercept	Modified HEK 293 and stable CHO cell lines	15.6 ng/mL-100 mg/mL elritercept	Elritercept inhibits SMAD2/3 signaling with greater potency than it inhibits SMAD1 signaling.
KT-240	The effect of a single dose of RKER-050 on hematopoiesis at days 37, 51, and 91	Mice/C57Bl6/Male (10)	RKER-050	Modified HEK 293 cells	0 and 10 mg/kg RKER-050, IP, once	RKER-050 significantly increased RBCs, HCT, and platelets at Days 37 and 51 compared to Veh, returning to Veh levels by Day 91. Serum EPO increased at Day 37 (4-fold, $p < 0.01$) but returned to baseline at 51 days.
KT-241	The acute 12 and 24 hr effect of RKER-050 on RBC volume and Hgb levels in WT mice	Mice/C57Bl6/Male (8-9)	RKER-050	Modified HEK 293 cells	0 and 10 mg/kg RKER-050, IP, once	RKER-050 significantly increased RBCs, Hgb, and HCT compared to Veh (all p -values < 0.05). Reductions in BM ProE and EryB at 12 hr leading to a large increase in EryC at 24 hr (all p -values < 0.050). No significant changes in EPO expression.

CONFIDENTIAL

Table A7 Summary of Nonclinical Pharmacology Studies of Elritercept/RKER-050

Study Number	Study Description	Species/Strain/Sex (N)	Drug	RKER-050/ Elritercept Source	Dose, Route, Duration	Results
KT-254	The effect of a single dose of RKER-050 on hematopoiesis at Day 2	Mice/C57Bl6/Male (10)	RKER-050	Modified HEK 293 cells	0 and 10 mg/kg RKER-050, IP, once	RKER-050 significantly increased RBCs, Hgb, and HCT compared to Veh (all p-values <0.050). Reductions in BM CFU-E, ProE, EryA, and EryB progenitors (all p-values <0.050).
KT-234	The effect of a single dose of RKER-050 on hematopoiesis at Day 7	Mice/C57Bl6/Male (6)	RKER-050	Modified HEK 293 cells	0 and 10 mg/kg RKER-050, IP, once	RKER-050 significantly increased RBCs, Hgb, and HCT compared to Veh (all p-values <0.050). BM progenitor cellularity replenishes in addition to elevated BM BFU-E and EryC progenitors (all p-values <0.050). Serum EPO elevated (3.2-fold, p <0.0001).
KT-235	The effect of a single dose of RKER-050 on hematopoiesis at Day 14	Mice/C57Bl6/Male (6)	RKER-050	Modified HEK 293 cells	0 and 10 mg/kg RKER-050, IP, once	RKER-050 significantly increased RBCs, Hgb, and HCT compared to Veh (all p-values <0.050). Elevated BM BFU-E, EryA, EryB, and EryC cells (all p-values <0.050). Reduced ProE (p <0.001) progenitors. Serum EPO elevated (2.5-fold, p <0.01).
KT-239	The effect of RKER-050 in NUP98/HOXD13 mice, a mouse model of MDS	Mice/C57Bl6/Male (6-10)	RKER-050	Modified HEK 293 cells	0 and 7.5 mg/kg RKER-050, IP, BIW for 39 days	Veh-treated NUP98/HOXD13 mice remained anemic throughout the study duration. RKER-050 treated NUP98/HOXD13 mice had significant increases in RBCs (+26.5%), Hgb (+17.0%), and HCT (+15%) on Day 39 (all p-values <0.050).

CONFIDENTIAL

Table A7 Summary of Nonclinical Pharmacology Studies of Elritercept/RKER-050

Study Number	Study Description	Species/Strain/Sex (N)	Drug	RKER-050/ Elritercept Source	Dose, Route, Duration	Results
KT-285	The effect of RKER-050 to ameliorate ruxolitinib-induced reductions in RBC volume, Hgb, and HCT	Mice/C57Bl6/ Female (5-10)	RKER-050	Modified HEK 293 cells	Ruxolitinib, 0, 90, and 120 mg/kg PO, BID for 55 days RKER-050 0 and 7.5 mg/kg, BIW for 14 days	Ruxolitinib dosing was associated with significant reductions in RBCs, Hgb, and HCT. Co-administration of RKER-050 mitigated these effects and significantly increased all three hematologic parameters.
KT-245	The efficacy of RKER-050 to increase hematologic parameters recovery after acute blood loss in rats	Rats/Sprague-Dawley/Male (4-5)	RKER-050	Modified HEK 293 cells	0 and 10 mg/kg RKER-050, SC, once	In the Veh-treated rats, significant recovery in Hgb and HCT was not observed until 6 days post blood loss compared to 24 hrs in the RKER-050 treated rats.
KT-374	Effects of chronic RKER-050 treatment in Gata-1 low mice, a model for myelofibrosis	Mice/mixed background (s129, C57BL/6 and CD-1)/male (10 per group)	RKER-050	Modified CHO cells	10 mg/kg BIW, IP, 8 weeks and 12 weeks	Treatment with RKER-050 resulted in complete correction of anemia as measured by RBC, HGB, and HCT after both 8 and 12 weeks of treatment, which was associated with a partial reversal of some perturbed erythroid (ProE, EryB, and RET) and MkP precursor cells in the bone marrow of Gata1low mice.

Table A7 Summary of Nonclinical Pharmacology Studies of Elritercept/RKER-050

Study Number	Study Description	Species/Strain/Sex (N)	Drug	RKER-050/ Elritercept Source	Dose, Route, Duration	Results
KT-469	Effects of RKER-050 in Gata-1 low mice treated with ruxolitinib	Mice/mixed background (s129, C57BL/6 and CD-1)/male (10 per group)	RKER-050	Modified CHO cells	10 mg/kg BIW, IP, 4 weeks	Administration of RKER-050 to Gata-1 low mice fully restored RBCs to WT levels. Gata-1 low mice treated with ruxolitinib showed a further decline in RBC parameters which were significantly reversed by RKER-050 treatment.
KT-273	The acute 24 hr effect of RKER-050 on RBC volume, Hgb, and PLT levels in WT mice	Mice/C57Bl6/Male (6)	RKER-050	Modified HEK-293 cells	0 and 10 mg/kg RKER-050, IP, once	RKER-050 significantly increased RBCs, Hgb, HCT, and PLTs compared to Veh (all p-values <0.050).
KT-94	Evaluating the efficacy of Keros Therapeutics test articles as a treatment for the lean mass loss in osteoporosis associated with androgen deficiency	Mice/C57B16/Male (sham and orchiectomized)	elritercept (ActRIIA/B-Fc)	Modified HEK-293 cells	0 and 20 mg/kg IP elritercept, BIW for 116 days	Elritercept treatment in both ORX and sham mice (p <0.0001 for both) led to significant increases in lean mass (18.2% in sham and 17.7% in ORX). ORX mice were osteoporotic at study start. KER050 treatment of sham and ORX mice resulted in significantly increased trabecular bone fraction and trabecular number.
KT-58	Identify effective doses of lean muscle gain and effects on bone structure and mass	Mice/C57Bl6/Male	elritercept (ActRIIA/B-Fc and ActRIIA/BA9-Fc)	Modified HEK-293 cells	0, 1, 3, 8 and 20 mg/kg IP elritercept, BIW for 27 days	Elritercept (ActRIIA/B-Fc) doses between 1 and 20 mg/kg led to increased body weight, lean mass and terminal muscle weight.

CONFIDENTIAL

Table A7 Summary of Nonclinical Pharmacology Studies of Elritercept/RKER-050

Study Number	Study Description	Species/Strain/Sex (N)	Drug	RKER-050/ Elritercept Source	Dose, Route, Duration	Results
KT-134	The effects of ActRIIA/B-Fc in aged MDX mice	Mice/C57B1/10 and MDX (12 RKER; 10 control)	RKER-050	Modified HEK-293 cells	0 and 20 mg/kg IP RKER-050, BIW for 81 days	RKER-050 improved body weight, lean mass, and muscle strength, and reduced muscle fibrosis in MDX mice.
KT-82	The effect of elritercept on development of retinal vasculature	Mice/CD-1/Male and Female (10 mouse pups per group; 15-18 retinas per group)	elritercept	Modified HEK-293 cells	0, 1 mg/kg (ActRIIB-Fc, elritercept), 10 mg/kg (ActRIIA-Fc, ActRIIB-Fc, and elritercept), SC, Days 1, 2, 3, and 5, 7-day duration	ActRIIB-Fc 10 mg/kg (positive control) increased vascular density ($p < 0.0001$). ActRIIB-Fc 10 mg/kg also had a significantly lower vascular front ratio than any other group. Both findings are evidence of BMP9 inhibition mediated disruption of vascular architecture. Treatment with elritercept or ActRIIA-Fc (negative control) did not result in vascular disruption, supporting lack of BMP9 inhibition by elritercept.
KRS01	The effect of elritercept on cytokine release	Homo sapiens/healthy blood/Male and Female (10)	elritercept	CHO Cells	0.5, 5, 50, 500 µg/mL	Overall, there were minimal changes in cytokine expression with elritercept (both Process I and II material), suggesting that elritercept is unlikely to trigger cytokine release in vivo. While one donor demonstrated a dose-related increase in IL-6 in the soluble format only, based on the totality of information available for elritercept, this finding is likely an artifact of human variability that is inherent in these assays as it was not observed across the other 9 donors, nor observed in the plate-based format.

Table A7 Summary of Nonclinical Pharmacology Studies of Elritercept/RKER-050

Study Number	Study Description	Species/Strain/Sex (N)	Drug	RKER-050/ Elritercept Source	Dose, Route, Duration	Results
KT-190	The effect of RKER-050 on cardiac function and remodeling in a mouse TAC model	Mouse/C57BL/6/ Male Vehicle (9) Preventative (11) Therapeutic (11)	elritercept	Transient HEK-293	10 mg/kg, subcutaneous, Vehicle: Day -7 to 56 (63 days) Preventative: Day -7 to 56 RKER-050 (63 days) Therapeutic: Day -7 to 28 (vehicle 35 days), Day 28 to 56 RKER-050 (28 days)	At both preventative and therapeutic dosing paradigms, RKER-050 prevented TAC-induced left ventricular hypertrophy and left ventricular dilation.
KTX-314	The effect of RKER-050 on hematopoiesis and skeletal mass in a murine model of Myelodysplastic syndromes (MDS)	Mice/C57BL/6 and MDS (C57BL/6 NUP98-HOXD13) Male Vehicle-WT (7) Therapeutic-WT (7) Vehicle-MDS (10) Therapeutic-MDS (9)	RKER-050	Transient HEK-293	7.5 mg/kg, IP Weekly Day 0 to 42	In both MDS and WT mice, once-weekly treatment with RKER-050 resulted in a statistically significant increase in body weight, red blood cell parameters and skeletal mass by Day 40. RKER-050 significantly reversed anemia and measurements of osteoporosis in MDS mice. In an MDS mouse model, RKER-050 can mitigate anemia and bone loss, potentially by rebalancing hematopoiesis and bone turnover.

elritercept is also referred to as ActRIIA/B-Fc.

CONFIDENTIAL

Appendix C STUDY KER050-MF-301 BASE STUDY TABLES

The following tables summarize information from the Base Study of Study KER050-MF-301, which includes data from the initial 24 weeks of study treatment.

Table A8 Overview of TEAEs in Dose Escalation Monotherapy (Safety Population; Study KER050-MF-301)

	Elritercept				Total (N=21) n (%)
	0.75 mg/kg (N=6) n (%)	1.5 mg/kg (N=6) n (%)	3.0 mg/kg (N=5) n (%)	4.5 mg/kg (N=4) n (%)	
Any TEAE	6 (100)	6 (100)	5 (100)	4 (100)	21 (100)
Any Treatment-Related TEAE	2 (33.3)	3 (50.0)	2 (40.0)	1 (25.0)	8 (38.1)
Any DLT	0	1 (16.7)	0	0	1 (4.8)
Any TESAE	2 (33.3)	2 (33.3)	4 (80.0)	2 (50.0)	10 (47.6)
Any Treatment Related TESAE	0	0	0	0	0
Any TEAE Leading to Death	0	0	1 (20.0)	1 (25.0)	2 (9.5)
Any TEAE Leading to Treatment Discontinuation	2 (33.3)	3 (50.0)	0	1 (25.0)	6 (28.6)
Any Grade ≥ 3 TEAE	4 (66.7)	4 (66.7)	5 (100)	2 (50.0)	15 (71.4)
Any Treatment-Related Grade ≥ 3 TEAE	0	0	1 (20.0)	0	1 (4.8)

Source: Table 14.3.1.1.BS

^a No DLTs reported by investigator, however, the SRC determined 1 participant in the monotherapy Dose level 1.5 mg/kg cohort had a dose-limiting event (Hgb increased).

Table A9 Overview of TEAEs in Dose Escalation Combination Therapy (Safety Population; Study KER050-MF-301)

	Elritercept + Ruxolitinib				
	0.75 mg/kg (N=6) n (%)	1.5 mg/kg (N=5) n (%)	3.0 mg/kg (N=5) n (%)	4.5 mg/kg (N=4) n (%)	Total (N=20) n (%)
Any TEAE	6 (100)	5 (100)	5 (100)	4 (100)	20 (100)
Any Treatment-Related TEAE	3 (50.0)	1 (20.0)	1 (20.0)	2 (50.0)	7 (35.0)
Any Elritercept-Related TEAE	2 (33.3)	0	1 (20.0)	1 (25.0)	4 (20.0)
Any Ruxolitinib-Related TEAE	2 (33.3)	1 (20.0)	1 (20.0)	1 (25.0)	5 (25.0)
Any DLT	0	0	0	0	0
Any TESAE	3 (50.0)	3 (60.0)	0	0	6 (30.0)
Any Elritercept-Related TESAE	0	0	0	0	0
Any Ruxolitinib Related TESAE	0	0	0	0	0
Any TEAE Leading to Death	1 (16.7)	0	0	0	1 (5.0)
Any TEAE Leading to Elritercept Discontinuation	2 (33.3)	1 (20.0)	0	0	3 (15.0)
Any TEAE Leading to Ruxolitinib Discontinuation	2 (33.3)	0	0	0	2 (10.0)
Any TEAE Leading to Ruxolitinib Dose Increase	0	0	0	0	0
Any Grade ≥ 3 TEAE	4 (66.7)	4 (80.0)	0	1 (25.0)	9 (45.0)
Any Treatment-Related Grade ≥ 3 TEAE	1 (16.7)	0	0	0	1 (5.0)
Any Elritercept-Related Grade ≥ 3 TEAE	1 (16.7)	0	0	0	1 (5.0)
Any Ruxolitinib -Related Grade ≥ 3 TEAE	1 (16.7)	0	0	0	1 (5.0)

Source: Table 14.3.1.1.BS

AEs were coded with MedDRA Dictionary version 24.0.

Table A10 TEAEs Reported in ≥10% Participants by Preferred Term in Dose Escalation Monotherapy (Safety Population; Study KER050-MF-301)

Preferred Term	elritercept 0.75 mg/kg (N=6) n (%)	elritercept 1.5 mg/kg (N=6) n (%)	elritercept 3.0 mg/kg (N=5) n (%)	elritercept 4.5 mg/kg (N=4) n (%)	elritercept Total (N=21) n (%)
Participants with ≥1 TEAE	6 (100)	6 (100)	5 (100)	4 (100)	21 (100)
Thrombocytopenia	1 (16.7)	2 (33.3)	2 (40.0)	3 (75.0)	8 (38.1)
Pyrexia	0	3 (50.0)	2 (40.0)	1 (25.0)	6 (28.6)
Asthenia	2 (33.3)	1 (16.7)	2 (40.0)	0	5 (23.8)
Diarrhoea	2 (33.3)	1 (16.7)	1 (20.0)	0	4 (19.0)
Arthralgia	1 (16.7)	2 (33.3)	0	0	3 (14.3)
Fatigue	2 (33.3)	1 (16.7)	0	0	3 (14.3)
Headache	1 (16.7)	1 (16.7)	0	1 (25.0)	3 (14.3)

Source: Table 14.3.1.5.BS

AEs were coded with MedDRA Dictionary version 24.0.

Table A11 TEAEs Reported in ≥10% Participants by Preferred Term in Dose Escalation Combination Therapy (Safety Population; Study KER050-MF-301)

Preferred Term	Elritercept + Ruxolitinib				
	0.75 mg/kg (N=6) n (%)	1.5 mg/kg (N=5) n (%)	3.0 mg/kg (N=5) n (%)	4.5 mg/kg (N=4) n (%)	Total (N=20) n (%)
Participants with at least 1 TEAE	6 (100)	5 (100)	5 (100)	4 (100)	20 (100.0)
Diarrhoea	3 (50.0)	4 (80.0)	0	0	7 (35.0)
Anaemia	0	1 (20.0)	0	2 (50.0)	3 (15.0)
Oedema peripheral	1 (16.7)	0	2 (40.0)	0	3 (15.0)
Urinary tract infection	1 (16.7)	1 (20.0)	0	1 (25.0)	3 (15.0)
Constipation	2 (33.0)	0	0	0	2 (10.0)
Dyspnoea	0	1 (20.0)	0	1 (25.0)	2 (10.0)
Epistaxis	0	1 (20.0)	1 (20.0)	0	2 (10.0)
Fall	0	0	0	2 (50.0)	2 (10.0)
Fatigue	1 (16.7)	1 (20.0)	0	0	2 (10.0)
Hypertension	1 (16.7)	1 (20.0)	0	0	2 (10.0)
Nausea	0	2 (40.0)	0	0	2 (10.0)
Pain in extremity	2 (33.3)	0	0	0	2 (10.0)
Thrombocytopenia	0	2 (40.0)	0	0	2 (10.0)

Source: Table 14.3.1.5.BS

AEs were coded with MedDRA Dictionary version 24.0.

CONFIDENTIAL

Table A12 Grade ≥ 3 TEAEs Reported in $\geq 10\%$ Participants by Preferred Term in Dose Escalation Monotherapy (Safety Population; Study KER050-MF-301)

Preferred Term	Elritercept				
	0.75 mg/kg (N=6)	1.5 mg/kg (N=6)	3.0 mg/kg (N=5)	4.5 mg/kg (N=4)	Total (N=21)
	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with ≥ 1 Grade ≥ 3 TEAE	4 (66.7)	4 (66.7)	5 (100.0)	2 (50.0)	15 (71.4)
Thrombocytopenia	1 (16.7)	2 (33.3)	2 (40.0)	2 (50.0)	7 (33.3)

Source: Table 14.3.1.7.BS

AEs were coded with MedDRA Dictionary version 24.0.

Table A13 Grade ≥ 3 TEAEs Reported in $\geq 10\%$ Participants by Preferred Term in Dose Escalation Combination Therapy (Safety Population; Study KER050-MF-301)

Preferred Term	Elritercept + Ruxolitinib				
	0.75 mg/kg (N=6)	1.5 mg/kg (N=5)	3.0 mg/kg (N=5)	4.5 mg/kg (N=4)	Total (N=20)
	n (%)	n (%)	n (%)	n (%)	n (%)
Participants with ≥ 1 Grade ≥ 3 TEAE	4 (66.7)	4 (80.0)	0	1 (25.0)	9 (45.0)
Thrombocytopenia [new]	0	2 (40.0)	0	0	2 (10.0)

Source: Table 14.3.1.7.BS

AEs were coded with MedDRA Dictionary version 24.0.

Table A14 TESAEs by Preferred Term in Dose Escalation Monotherapy (Safety Population; Study KER050-MF-301)

Preferred Term	Elritercept				Total (N=21) n (%)
	0.75 mg/kg (N=6) n (%)	1.5 mg/kg (N=6) n (%)	3.0 mg/kg (N=5) n (%)	4.5 mg/kg (N=4) n (%)	
Participants with ≥ 1 TESA	2 (33.3)	2 (33.3)	4 (80.0)	2 (50.0)	10 (47.6)
Pneumonia	0	1 (16.7)	0	1 (25.0)	2 (9.5)
Acute myeloid leukaemia	0	0	0	1 (25.0)	1 (4.8)
Cardiac failure	1 (16.7)	0	0	0	1 (4.8)
Catheter site cellulitis	1 (16.7)	0	0	0	1 (4.8)
Chronic obstructive pulmonary disease	1 (16.7)	0	0	0	1 (4.8)
Infection	0	1 (16.7)	0	0	1 (4.8)
Melaena	0	0	1 (20.0)	0	1 (4.8)
Multiple organ dysfunction syndrome	0	0	0	1 (25.0)	1 (4.8)
Pneumonia aspiration	0	0	1 (20.0)	0	1 (4.8)
Pyrexia	0	0	1 (20.0)	0	1 (4.8)
Rectal haemorrhage	0	0	1 (20.0)	0	1 (4.8)
Upper limb fracture	0	1 (16.7)	0	0	1 (4.8)
Visual impairment	0	0	0	1 (25.0)	1 (4.8)

Source: Table 14.3.2.1.BS

AEs were coded with MedDRA Dictionary version 24.0.

Table A15 **TESAEs by Preferred Term in Dose Escalation Combination Therapy**
(Safety Population; Study KER050-MF-301)

Preferred Term	Elritercept + Ruxolitinib				Total (N=20) n (%)
	0.75 mg/kg (N=6) n (%)	1.5 mg/kg (N=5) n (%)	3.0 mg/kg (N=5) n (%)	4.5 mg/kg (N=4) n (%)	
Participants with ≥ 1 TESAE	3 (50.0)	3 (60.0)	0	0	6 (30.0)
Abdominal infection	0	1 (20.0)	0	0	1 (5.0)
Cerebrovascular accident	1 (16.7)	0	0	0	1 (5.0)
Diarrhoea	0	1 (20.0)	0	0	1 (5.0)
Peritonitis	0	1 (20.0)	0	0	1 (5.0)
Respiratory syncytial virus infection	0	1 (20.0)	0	0	1 (5.0)
Sinusitis fungal	1 (16.7)	0	0	0	1 (5.0)
Transformation to acute myeloid leukaemia	1 (16.7)	0	0	0	1 (5.0)
Transient ischaemic attack	1 (16.7)	0	0	0	1 (5.0)
Vomiting	0	1 (20.0)	0	0	1 (5.0)

Source: Table 14.3.2.1.BS

AEs were coded with MedDRA Dictionary version 24.0.

Signature Page for Elritercept IB Edition 8
Title: Elritercept Investigator's Brochure Edition 8

Approval Task	Leopold Sellner leopold.sellner@takeda.com Clinical 02-Jul-2025 13:28:21 GMT+0000
---------------	--

Approval Task	Haig Inguilizian Haig.Inguilizian@takeda.com Pharmacovigilance 02-Jul-2025 14:10:47 GMT+0000
---------------	---

Document Number: TDN-000530406 v2.0