CLINICAL STUDY PROTOCOL

A phase II study evaluating the efficacy and safety of IMetelstat in Patients with HR myElodysplastic SyndromeS or AML failing HMA-based therapy

IMpress Study

STUDY DRUG(s):	**Imetelstat**
SHORT TITLE:	**IMpress**
PROTOCOL CODE:	**IMpress_001**
EUCT NUMBER:	2022-500721-32
VERSION:	**6.0 NCT05583552**
DATE:	**03.09.2025 NCT05583552**

This protocol was created in cooperation with

EMSCO European Myelodysplastic Syndromes Cooperative Group

D·MDS Deutsche MDS-Studiengruppe

gfm Groupe Francophone des Myélodysplasies

ALLG Australasian Leukaemia & Lymphoma Group

I. Amendments

Version	Description	Date
1.0	Initial version	19-AUG-2022
2.0	Non-substantial changes only • Removed certain procedures from schedule of assessments: ○ [redacted] ○ BMA sampling for central laboratory [redacted], ○ central laboratory assays at [redacted], ○ buccal swab/hair follicle sampling • Changes for clarification of information or to correct minor errors, including formatting and grammar, and to correct inconsistencies between different sections of the protocol.	09-DEC-2022
3.0	Non-substantial changes only • Removal of the references to AESI and related form (Imetelstat Questionnaire for AESI) under dose modifications for hepatic toxicities. • Addition of serum chemistry in schedule of assessments for patient safety monitoring: ○ At C1W1, C2W5, C4W13, C6W21, C8W29, C9W33. • Changes for clarification of information or to correct minor errors, including formatting and grammar. • Updated sponsor logo inserted	25-JAN-2023
4.0	Non-substantial changes only • Amended information based on updated Investigator's Brochure from version 18 to 19. • Secondary efficacy endpoint added for response based on IWG 2023 criteria. • Changes for clarification of information or to correct minor errors, including formatting and grammar.	19-SEP-2023
5.0	**Substantial modification** [redacted] • Amended treatment regimen from every [redacted] weeks to every [redacted] weeks for the first [redacted] cycles. Amendments in sections 5, 7, 8 and 10 to reflect this.	13-MAY-2024

	• Defined responder status as 2 types based on BM blast levels. Amendments in sections 5, 7 and 8 to reflect this. • Added a guideline to stop treatment if signs of disease progression on bone marrow after 4 doses of treatment. Amendments in sections VII, 5.1.3, 7.1 and 8.1.4 to reflect this. • Where dosage is mentioned, imetelstat has been changed to imetelstat sodium for clarity. • Changes for clarification of information or to correct minor errors, including formatting and grammar. • Section I Amendments created. • Section VII: Schedule of assessments and procedures amended • Section 1.3 Risk benefit assessment amended. • Section 4.2 Data monitoring amended and a risk-benefit assessment to be performed after 10 patients are enrolled added. • Section 6.3: added inclusion criterion number 17. • Section 7.1 amended and subsection 7.1.1 Treatment regimen prior to amendment to protocol version 5.0 created. • Section 7.6 Selection of doses in the study amended. • Section 7.9 Prestudy and concomitant medication was amended. • Section 9 Safety was amended for clarifications on the use of certain terminology in AE reporting and new AESIs were added. • Section 9.7 Reporting of serious breaches was created.	
6.0	Substantial modification • Clarification on treatment in the extension phase for non-responders with stable or controlled disease. • Addition of a schedule of assessments for the extension treatment phase, applicable to non-responders with stable or controlled disease who remain on treatment (Part 2c) • Update of the CPI contact information • Minor errors, including formatting and grammar corrected.	03-SEP-2025

II. Signatures

SPONSOR SIGNATURE PAGE

Sponsor:

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Signature of Sponsor's Representative | Date

Dr. Andreas Beust

Printed Name of Representative

By my signature, I agree to supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines or local regulations governing the conduct of clinical studies.

COORDINATING INVESTIGATOR SIGNATURE PAGE
- GLOBAL LEAD AND NATIONAL COORDINATOR GERMANY -

Coordinating Investigator	Uwe Platzbecker, MD Universitätsklinikum Dresden Medizinischer Vorstand Fetscherstraße 74 01307 Dresden, Germany [redacted]

Signature of Coordinating Investigator Date

Prof. Dr. med. Uwe Platzbecker

Printed Name of Coordinating Investigator

By my signature, I agree to conduct this study according to this protocol and to make no additions or changes without the consent of the sponsor. In addition, I agree that the study will be carried out in accordance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with the laws and regulations of the country in which the study takes place.

III. Synopsis

Title	A phase II study evaluating the efficacy and safety of imetelstat in patients with HR myelodysplastic syndromes or AML failing HMA-based therapy
Short title	IMpress
Indication	AML and MDS patients failing or being refractory to hypomethylating agent (HMA)-based treatment
Phase	II
Study design	Open-label, single-arm multicenter, phase II study
Participating centers	Germany, France, Australia 12 sites (4 Germany, 4 France, 4 Australia)
Number of subjects	[redacted] to end up with [redacted] evaluable subjects ([redacted] drop-out rate)
Background and hypothesis of the trial	Imetelstat (GRN163L) is a covalently-lipidated 13-mer thiophosphoramidate oligonucleotide that acts as a potent specific inhibitor of telomerase. Treatment of various cancer cells with Imetelstat in vitro increases their sensitivity to radiation, decreases their clonogenic potential, and results in altered expression of stem-cell related genes. Data from a phase II study as well as cytogenetic and mutational data for lower risk MDS provide an encouraging basis for further investigation of the agent in higher risk MDS and AML patients ineligible for allo-HSCT, constituting entities with an even greater need for new therapeutic options.
Planned interventions	All patients will receive 2-hour intravenous (IV) infusion with Imetelstat [redacted] in a [redacted] cycle (once every [redacted] days) for at least [redacted] cycles. After [redacted] treatment cycles ([redacted] administrations of Imetelstat) response assessment will be performed on all patients. Non-responding patients will discontinue Imetelstat treatment, undergo EOT and enter the follow-up phase of the trial. Patients who are categorized as responders according to the primary endpoint definition and have BM blasts ≥5% at the response assessment [redacted] will continue Imetelstat treatment every [redacted] days until loss of response/disease progression. Patients who are categorized as responders according to the primary endpoint definition and have BM blasts <5% will continue Imetelstat treatment every [redacted] days until loss of response/disease progression.
Ethical considerations	There are currently very few licensed drugs in the EU to treat MDS or AML patients having failed or being refractory to treatment with HMAs. Furthermore, allo-HSCT can be offered only to a minority of those patients. Therefore, new treatment options are urgently needed for this patient cohort. Imetelstat, a first-in-class telomerase inhibitor, with its novel mechanism of action, may provide clinical benefit to MDS and AML patients. First clinical trial results suggest an activity in lower risk MDS and good tolerability.

Study objective(s)	**Primary:** To assess the efficacy of Imetelstat for the treatment of AML and MDS patients failing or being refractory to hypomethylating agent (HMA)-based treatment **Secondary:** **Safety objective:** • Toxicity as measured by NCI CTCAE v5.0 **Efficacy objective:** • Overall survival • Progression-free-survival • Duration of response • Best overall response • Quality of Life (EORTC QLQ-C30)

Study endpoints	**Primary:**
	• Overall response rate assessed after 4 months of treatment
	  • Using combined response assessment criteria for MDS and AML based on IWG 2018 criteria (MDS)[1] and the criteria of the European LeukemiaNet (AML)[2], as defined in Appendix III a), section 16.3.
	
	Secondary:
	<u>Safety Measurements</u>
	• Toxicity as measured by NCI CTCAE v5.0
	
	<u>Efficacy Measurements</u>
	• Overall survival
	  • defined as the time from the beginning of imetelstat treatment until death or censored at the date of the last follow-up visit.
	• Progression-free-survival
	  • defined as the duration of time from time of imetelstat treatment to time of progression or death, whichever occurs first. A subject who has neither progressed nor died will be censored on the date of last follow-up visit.
	• Duration of best overall response
	  • measured from the time measurement criteria are met for CR, CRi, PR or SD (whichever is recorded first, defined in Appendix III a), section 16.3) until the first date at which recurrent or progressive disease is objectively documented.
	• Best overall response
	  • defined as the best response recorded from the start of the imetelstat treatment until disease progression (taking as reference for progressive disease the smallest measurements recorded since the treatment started).
	• Response based on IWG 2023 criteria (MDS population only)
	  • assessed in week [redacted] of treatment with imetelstat, for definition see Appendix III b).
	• Scores of EORTC QLQ-C30 (version 3)
	  • Global health status / QoL
	  • Functional scales
	  • Symptom scales / items

Medical condition	AML and MDS patients failing or being refractory to hypomethylating agent (HMA)-based treatment
Eligibility criteria	**Inclusion criteria:** 1 Signed written informed consent 2 Male and female ≥ 18 years at the first screening 3 Must be able to adhere to the study visit schedule and other protocol requirements 4 Initial diagnosis of AML or MDS according to WHO 2016 classification 5 At least one cytopenia (ANC < [redacted]/µL or platelet count < [redacted]/µL or hemoglobin < [redacted] g/dL) 6 a. Failure to achieve complete or partial response or hematological improvement observed after at least six azacitidine monotherapy or four decitabine monotherapy based 4-week treatment cycles administered during the past two years OR b. Failure to achieve complete or partial response or hematological improvement observed after at least two 4-week treatment cycles with azacitidine plus venetoclax or with decitabine plus venetoclax during the past two years OR c. Relapse after initial complete or partial response or hematological improvement observed after at least six (azacitidine) or four (decitabine) based 4-week treatment cycles administered during the past two years OR d. Relapse after initial complete or partial response or hematological improvement observed after at least two 4-week treatment cycles with azacitidine plus venetoclax or with decitabine plus venetoclax during the past two years OR e. Intolerance to treatment with HMA-based therapy during the past two years 7 Not eligible for allogeneic stem cell transplantation 8 ≥ 5% bone marrow blasts at screening 9 Off all other treatments for AML/MDS for at least 14 days; G-CSF and erythropoietin are allowed before and during the study as clinically indicated 10 ECOG performance status of 0-2 11 Biochemical laboratory test values must be within the following limits: [redacted]

	[redacted] 12 Availability of blood counts and transfusion events for previous 16 weeks 13 Women of childbearing potential and practicing a highly effective method of birth control according to the Clinical Trial Facilitation Coordination Group Recommendation (Version 1.1, 2020)[28]: - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: o oral o intravaginal o transdermal - progestogen-only hormonal contraception associated with inhibition of ovulation: o oral o injectable o implantable - intrauterine device (IUD) - intrauterine hormone-releasing system (IUS) - bilateral tubal occlusion - vasectomised partner - sexual abstinence For females, these restrictions apply for 3 months after the end of dosing. Note: If the childbearing potential changes after start of the study (e.g., woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) a woman must begin a highly effective method of birth control, as described above 14 A woman of childbearing potential must have a negative serum (ß-human chorionic gonadotropin [ß-hCG] pregnancy test at screening and agree to be tested (serum or urine) on day 1 of every cycle and at EOT 15 A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study. For males, these restrictions apply for 3 months after the end of dosing 16 France-specific inclusion criterion: Subjects participating at French sites must be covered by the French public welfare system. 17 Patients who are relapsed or refractory to, or not eligible for, therapy with approved and available FLT3 or IDH1/IDH2 inhibitors or other approved targeted therapies.

Eligibility criteria	**Exclusion criteria** 1 Chemotherapy within the 14 days prior to the first dose of imetelstat being administered (other than hydroxyurea) 2 Subject has known allergies, hypersensitivity, or intolerance to imetelstat or its excipients (refer to the IB) 3 Subject has received an experimental or investigational drug or used an invasive investigational medical device within 30 days prior to day 1 of C1 4 Prior treatment with imetelstat 5 Prior history of intensive chemotherapy or hematopoietic stem cell transplant 6 Major surgery within 4 weeks prior to day 1 of C1 (excluding the placement of vascular access and other minor surgical procedures) 7 Diagnosed or treated for malignancy other than MDS or AML, except: a. Malignancy treated with curative intent and with no known active disease present for 3 years before day 1 of C1 b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease c. Adequately treated cervical carcinoma in situ without evidence of disease 8 Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of day 1 of C1, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification 9 Known history of human immunodeficiency virus (HIV) or any uncontrolled active systemic infection requiring IV antibiotics 10 Active systemic hepatitis infection requiring treatment (carriers of hepatitis virus are permitted to enter the study), or known acute or chronic liver disease including cirrhosis 11 Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the imetelstat metabolism, or put the study outcomes at undue risk; Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments 12 Females who are pregnant or are currently breastfeeding or planning to become pregnant while enrolled in this study or within 3 months after the end of dosing 13 Subject is a man who plans to father a child while enrolled in this study or within 3 months after the end of dosing 14 Subject is in custody by order of an authority or a court of law 15 Previous assignment to treatment during this study

	16 Close affiliation with the investigator (e.g., a close relative) or persons working at the study site 17 Subject is an employee of the sponsor or involved CRO 18 Criteria which in the opinion of the investigator preclude participation for scientific reasons, for reasons of compliance, or for reasons of the subject's safety
Study treatment(s)	Test drug: Imetelstat sodium Starting dose: [redacted] Dosing regimen: [redacted] until disease progression, unacceptable toxicity, withdrawal of consent, or lack of response. Responding patients at cycle [redacted] (defined as CR [complete remission], CRi [CR with incomplete hematologic recovery] or PR [partial remission] and/or showing a hematologic improvement for one or several lines) are eligible to continue treatment. Responding patients who have BM blasts ≥5% at the response assessment [redacted] will continue Imetelstat treatment every [redacted] days until loss of response/disease progression. Responding patients who have BM blasts <5% will continue Imetelstat treatment every [redacted] days until loss of response/disease progression. Non-responding patients will discontinue Imetelstat treatment, undergo EOT and enter the follow-up phase of the trial. Administration route: Intravenous (IV)

Time plan	<u>For the individual patient</u>: • Minimum of 4 months of treatment every [redacted] weeks (until primary endpoint assessment). • For responders with BM blasts ≥5% at the response assessment [redacted]: treatment every [redacted] weeks until loss of response / progression, followed by 3 months of follow-up. • For responders with BM blasts <5% at the response assessment (V9); treatment every 4 weeks until loss of response / progression, followed by 3 months of follow-up. • For Non-responders: treatment stopped after 4 months/cycles followed by 3 months of follow-up. In the absence of alternative treatment options, non-responders with stable or controlled disease may continue treatment in the extension phase at the investigator's discretion, in consultation with the sponsor, provided the disease remains controlled and none of the discontinuation criteria are met. <u>Planned study schedule</u>: First Patient First Visit (actual) [redacted] Last Patient First Visit [redacted] Last Patient End of Treatment [redacted] Last Patient End of Study [redacted] Clean database [redacted]* Final Study report [redacted] * best estimate as treatment until loss of response / progression

Sample size	The study was designed as single-arm phase II trial. The design of the trial focused on demonstrating that the efficacy is greater than an undesired level of efficacy (p_0) which would indicate that the treatment is ineffective. A Simon's two-stage design was used to allow for initial assessment of efficacy. The sample size calculation was based on the following assumptions. • Given Null hypothesis H_0: $p \leq p_0$ • Alternative hypothesis H_1: $p > p_0$ • Level of inefficacy $p_0 = 0.05$ • Expected true response rate $p_1 = 0.2$ • Type-1-error $\alpha = 0.05$, one-sided • Type-2-error ß = 0.1 The null hypothesis that the true response rate is 0.05 was planned to be tested against a one-sided alternative. In the first stage, [redacted] patients were accrued. If there were 1 or fewer responses in these [redacted] patients, the study should be stopped. Otherwise, it was planned to accrue [redacted] additional patients for a total of [redacted] The null hypothesis would be rejected in favor of the alternative hypothesis if 5 or more responses are observed in [redacted] patients. This design yielded a one-sided type I error rate of no more than 0.05 and power of at least 0.9 when the true response rate is 0.2. To account for a loss of follow up of ~10%, enrollment of up to [redacted] patients is expected. Similarly, a total of [redacted] patients were planned to be enrolled prior to the interim analysis to ensure [redacted] evaluable patients for the interim analysis. [redacted] the study will continue in an exploratory approach with a change in dose frequency.
Financing	The study is financially supported by Geron Corporation.

IV. Contacts and responsibilities

Sponsor	GCP-Service International West GmbH Siegfeldstraße 11 53721 Siegburg/Germany Phone: +49 (0) 421 89 67 66 11 E-Mail: germany@gcp-service.com
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	01307 Dresden, Germany [redacted]
National Coordinating Investigator France	Prof. Lionel Adès Service d'hématologie seniors Hôpital Saint-Louis Trèfle 4 1 Avenue Claude Vellefaux 75010 Paris, France [redacted]
National Coordinating Investigator Australia	[redacted]
Study Groups	German MDS Study Group (D-MDS) Groupe Francophone des Myélodysplasies (GFM) Australasian Leukaemia & Lymphoma Group (ALLG)
Protocol Committee	• [redacted] University Hospital Dresden, Germany • [redacted] Hopital Saint Louis, Service d'hématologie Séniors, France • [redacted] • [redacted] University Hospital Leipzig, Germany
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V. Table of contents

V.a) List of tables

V.b) List of figures

VI. Abbreviations

ADR	Adverse drug reaction
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUS	Australia
AZA	5-azacytidine
ß-HCG	Beta human chorionic gonadotropin
BM	Bone marrow
BMI	Body Mass Index
BSC	Best supportive care
C1D1	Cycle 1 Day 1
CBC	Complete blood count
CI	Confidence Interval
CPI	Coordinating Principal Investigator (*Leiter der klinischen Prüfung*)
CR	Complete Remission
CRi	Complete Remission with Incomplete hematologic recovery
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-Drug Interaction
DLT	Dose Limiting Toxicity
DM	Data Manager
DMP	Data Management Plan
DMC	Data monitoring committee
DSUR	Development Safety Update Report
DVP	Data Validation Plan
EC	Ethics committee
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status

eCRF	Electronic case report form
EOS	End of Study
EOT	End of Treatment
ESA	Erythropoiesis-stimulating agents
EU	European Union
FAS	Full analysis set
FCBP	Female of childbearing potential
FU	Follow-up
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
Hb	Hemoglobin
HI	Hematologic Improvement
HI-E	Hematological improvement - erythroid
HI-N	Hematological improvement - neutrophils
HI-P	Hematological improvement - platelets
HMA	Hypomethylating agents
HR MDS	Higher Risk Myelodysplastic syndromes
HSCs	Hematopoietic stem cells
hTERT	human Telomerase Reverse Transcriptase
hTR	human Telomerase Ribonucleic acid template
IB	Investigators Brochure
ICF	Informed consent form
ICMJE	International Committee of Medical Journal Editors
ICT	Iron chelation therapy
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
IPSS-R	International Prognostic Scoring System-Revised
ISF	Investigator site file
IWG	International Working Group
LDH	Lactate Dehydrogenase
LEN	Lenalidomide
LFT	Liver function test
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration

MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MDS-RS	MDS with ring-sideroblastic phenotype
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic Leukemia-Free State
NCI	National Cancer Institute
NGS	Next Generation Sequencing
nRBC	nucleated Red Blood Cells
OS	Overall survival
ORR	Overall Response Rate
PB	Peripheral blood
PD	Progressive Disease
pEP	primary Endpoint
PFS	Progression-Free Survival
PPS	Per Protocol Set
PR	Partial Remission
pRBCs	Packed red blood cells
q3w	Every three weeks
QIMRB	Queensland Institute of Medical Research Berghofer
QoL	Quality of life
RBC	Red blood cell
RDW	Red blood cell distribution width
RNA	Ribonucleic Acid
RS	Ring sideroblasts
RSI	Reference safety information
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Statistical Analysis Report
SC	Subcutaneous
SD	Stable Disease
SES	Safety Evaluation Set
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase

SPM	Secondary primary malignancies
SUSAR	Suspected unexpected serious adverse reaction
TEAEs	Treatment emergent adverse events
TI	Transfusion Independency
TL	Telomere Length
TMF	Trial master file
ULN	Upper limit of normal
VEN	Venetoclax
WBC	White blood cell count
WHO	World Health Organization

VII. Schedule of assessments and procedures

Part 1 – primary treatment phase, cycles 1-4 (all patients)

VISIT NO.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Day[1] **(± 3d)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Week		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Informed consent	x											
In- / exclusion criteria[3]	x	x										
MDS/AML related medical history	x											
Concomitant medication and previous MDS/AML specific medication	x									x		
Concomitant MDS/AML specific medication		x		x		x		x		x		
Physical examination, vitals	x	x	x	x	x	x	x	x	x	x	x	x
ECOG performance status	x									x		
BMI	x					x				x		
ECG	x											
Pregnancy test[4]	x	x		x		x		x		x		
Imetelstat administration[5] and drug account		x	x	x	x	x	x	x	x	x[6]	x[7]	
Toxicity/AE assessment	x	x	x	x	x	x	x	x	x	x	x	
Quality of life (QoL, EORTC QLQ-C30)	x	x		x		x		x		x		

[1] All visits will be carried out in a timeframe of ± 3 days of the mentioned visit date

[2] Screening period starts with the day of consent and all screening procedures must be completed within up to 35 days prior to the first dose (except baseline measure of cytogenetics)

[3] Pretreatment baseline measures of cytopenias are averages of at least 2 measurements over at least one week prior to therapy

[4] Pregnancy tests for verification of in-/exclusion criteria prior to starting with study medication / inclusion with a minimum sensitivity of 25 mIU/mL for women of child-bearing potential only is to be done not more than 3 days prior to initiation of treatment. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is required. This requirement also applies to women of childbearing potential with infrequent or irregular menstrual cycles.

[5] Imetelstat sodium will be administered at a starting dose of [redacted] mg/kg given intravenously every [redacted] weeks for the first [redacted] cycles of treatment.

[6] Treatment with imetelstat will be continued until results of response assessment are available

[7] Imetelstat administration at this visit only for responders with ≥5% BM blasts.

LOCAL LABORATORY: Response assessment[8]						x[9]				x	
Central assessments / correlative analyses (EU: Leipzig, AUS: QIMRB, Brisbane)											
Bone marrow aspiration (5 mL sodium heparinized in separate tubes for central assessments)	x					x				x	
Peripheral blood sampling for central assessments (10 mL sodium heparinized blood in separate tubes for central assessments)	x					x				x	
Genetic profiling (NGS) at central laboratories	x									x	
MRD analyses at central laboratories						x				x	
Telomere profiling at central laboratories	x										
Telomere length at central laboratories	x									x	
Study-specific biomaterial collection	x					x				x	
Local assessments											
CBC with differential (local)	x					x				x	
PB blast assessment (local)	x			x		x		x		x	
BM cytology assessment (local)[10]	x					x				x	
Serum chemistry (local)	x	x		x		x		x		x	
Automated CBC (local)	x	x	x	x	x	x	x	x	x	x	x
Cytogenetics (local)	x					x				x	

[8] Response assessment will be performed based on the combined response assessment criteria for MDS and AML based on IWG 2018 criteria (MDS) and the criteria of the European LeukemiaNet (AML) in [redacted] after ending [redacted] (see Appendix III, section 16.3). Response assessment period lasts until all necessary lab results are available and can be assessed. Meanwhile patients further receive IMP until result of response assessment are present (starting [redacted]). Results of response assessment are the basis for further treatment or proceeding to EOT. Additionally, the BM blast levels at each response assessment from cycle 5 will be the basis for deciding the frequency of treatment of imetelstat (every [redacted] weeks or every [redacted] weeks) until the next response assessment.

[9] If signs of disease progression are present in bone marrow at the response assessment after 4 doses with imetelstat, treatment with imetelstat must be discontinued and the patient to undergo EOT.

[10] A BM biopsy is to be collected when adequate aspirate is not attainable or if the BM aspirate shows fewer than 5% bone marrow blasts. Whenever a BM sample is collected, both BM and PB smears are to be prepared.

Part 2a – extension treatment phase, from cycle 5 until loss of response / disease progression (**responders with BM blasts <5% only**)

VISIT NO.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Day (± 3d)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Informed consent									
In- / exclusion criteria[3]									
MDS/AML related medical history									
Concomitant MDS/AML specific medication	x		x		x		x		x
Physical examination, vitals	x	x[11]	x	x[11]	x	x[11]	x	x	x
ECOG performance status									
BMI			x						
Pregnancy test[4]	x		x		x		x		x
Imetelstat administration[5] and drug account	x		x		x		x[6]		x[12]
Toxicity/AE assessment	x	x[11]	x	x[11]	x	x[11]	x	x	x
Quality of life (QoL, EORTC QLQ-C30)	x		x		x		x	x	x
LOCAL LABORATORY: Response assessment[8]			x					x	x[13]
Central assessments / correlative analyses (EU: Leipzig, AUS: QIMRB, Brisbane)									
Bone marrow aspiration (5 mL sodium heparinized in separate tubes for central assessments)			x						
Peripheral blood sampling for central assessments (10 mL sodium heparinized blood in separate tubes for central assessments)			x						
Genetic profiling (NGS) at central laboratories									
MRD analyses at central laboratories			x						

11 Can be done at patient's general practitioner practice at investigator's discretion (for non-treatment visits only)

12 If a patient is responding to imetelstat and continues beyond [redacted], each disease assessment should determine whether treatment with imetelstat is given every [redacted] weeks (responding with ≥5% BM blasts) or every [redacted] weeks (responding with <5% BM blasts).

13 Response assessment every 3 months (when BM cytomorphology is carried out)

Telomere length & telomerase profiling at central laboratories									
Study-specific biomaterial collection			x						
Local assessments									
CBC with differential (local)			x					x[14]	x[15]
PB blast assessment (local)	x		x		x		x	x[14]	x[15]
BM cytology assessment (local)[10]			x					x[14]	x[15]
Serum chemistry (local)	x		x		x		x	X	x
Automated CBC (local)	x	x[11]	x	x[11]	x	x[11]	x	x	x
Cytogenetics (local)			x					x	

[14] Only to be carried out if the last assessment is more than 14d apart

[15] BM / CBC assessment every 3 months and at every timepoint of suspected progression starting [redacted] weeks after last morphology assessment at [redacted]

Part 2b – extension treatment phase, from cycle 5 until loss of response / disease progression (**responders with BM blasts ⩾5% only**)

VISIT NO.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Day (± 3d)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Week	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Informed consent									
In- / exclusion criteria[3]									
MDS/AML related medical history									
Concomitant MDS/AML specific medication	x		x		x		x		x
Physical examination, vitals	x	x	x	x	x	X	x	x	x
ECOG performance status									
BMI			x						
Pregnancy test[4]	x		x		x		x		x
Imetelstat administration[5] and drug account	x	x	x[6]	x	x	x	x	x	x[12]
Toxicity/AE assessment	x	x	x	x	x	x	x	x	x
Quality of life (QoL, EORTC QLQ-C30)	x		x		x		x	x	x
LOCAL LABORATORY: Response assessment[8]			x					x	x[13]
Central assessments / correlative analyses (EU: Leipzig, AUS: QIMRB, Brisbane)									
Bone marrow aspiration (5 mL sodium heparinized in separate tubes for central assessments)			x						
Peripheral blood sampling for central assessments (10 mL sodium heparinized blood in separate tubes for central assessments)			x						
Genetic profiling (NGS) at central laboratories									
MRD analyses at central laboratories			x						
Telomere length & telomerase profiling at central laboratories									
Study-specific biomaterial collection			x						
Local assessments									
CBC with differential (local)			x					x[14]	x[15]
PB blast assessment (local)	x		x		x		x	x[14]	x[15]
BM cytology assessment (local)[10]			x					x[14]	x[15]
Serum chemistry (local)	x		x		x		x	x	x
Automated CBC (local)	x	x	x	x	x	x	x	x	x
Cytogenetics (local)			x					x	

Part 2c – extension treatment phase, from cycle 5 **(non-responders with stable or controlled disease who continue treatment at the investigator's discretion)**

VISIT NO.	[redacted]
Study Day (± 3d)	[redacted]
Study Week	[redacted]
Cycle	[redacted]
Concomitant MDS/AML specific medication	**x**
Pregnancy test	**x**
Imetelstat administration and drug account	**x**[16]
Toxicity/AE assessment	**x**
LOCAL LABORATORY: Response assessment[17]	**x**[18]
CBC with differential (local)	**x**[18]
PB blast assessment (local)	**x**[18]
BM cytology assessment (local)	**x**[18]

16 The dosing frequency for imetelstat (every [redacted] weeks or every [redacted] weeks) for these subjects will be determined at the discretion of the investigator.

17 Response assessment will be performed based on the combined response assessment criteria for MDS and AML based on IWG 2018 criteria (MDS) and the criteria of the European LeukemiaNet (AML). Additionally, the BM blast level at each response assessment will be the basis for deciding the frequency of treatment of imetelstat (every [redacted] weeks or every [redacted] weeks) until the next response assessment.

18 Optional response assessment and lab measurements to be done according to standard of care and/or only in case needed to assess and follow-up on (S)AEs and dose modifications

Part 3 – EOT and follow-up period (all patients)

VISIT NO.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Day (± 3d)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study Week	[redacted]				
Informed consent					
In- / exclusion criteria[3]					
MDS/AML related medical history					
Concomitant MDS/AML specific medication	x	x	x	x	
Physical examination, vitals	x	x	x	x	
BMI	x	x	x	x	
Pregnancy test[4]	x	x	x	x	
Toxicity/AE assessment	x	x	x	x	
Quality of life (QoL, EORTC QLQ-C30)	x	x	x		
Information on current state of condition / survival status	x	x	x	x	x
Central assessments / correlative analyses (EU: Leipzig, AUS: QIMRB, Brisbane)					
Bone marrow aspiration (5 mL sodium heparinized in separate tubes for central assessments)		x[22]			
Peripheral blood sampling for central assessments (10 mL sodium heparinized blood in separate tubes for central assessments)		x[22]			
Genetic profiling (NGS) at central laboratories		x			
MRD analyses at central laboratories					
Telomere length & telomerase profiling at central laboratories		x			
Study-specific biomaterial collection		x			
Local assessments					
Serum chemistry (local)	x	x	x		
Automated CBC (local)	x	x	x		

19 FU2/EOS can be carried out on the telephone

20 To be carried out once the results of the response assessment from [redacted] are available and at the latest 14 days after the date of decision of treatment discontinuation

21 Responders after the assessment at [redacted] will be treated further until loss of response/disease progression. In the case of safety issues, loss of response or disease progression, patients will undergo the EOT visit within 14 days from the date of decision of treatment discontinuation.

22 BM and PB sample collection should only be performed at EOT visit if > 90 days from prior BM procedure

1 Scientific background and rationale

1.1 Introduction

1.1.1 Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML)

Myelodysplastic syndromes constitute a heterogeneous form of blood cancer that primarily affects the elderly and are characterized by anemia and other cytopenias and a high risk of leukemic transformation[3]. In routine clinical practice, MDS are suspected when an otherwise unexplained anemia is associated with other cytopenias, increased mean corpuscular volume, or increased red cell distribution width. Diagnosis requires bone marrow examination and cytogenetic studies. The bone marrow is typically hyperproliferative. The diagnosis is based on demonstration of erythroid, granulocyte, or megakaryocyte dysplasia in 10% or more of informative cells[4]. The natural history of MDS includes transformation to AML in a proportion of patients.

Especially for patients with higher risk MDS there is an increased risk of progression to AML. The transition between the two diseases is often fluent and, as a main criterion, based on the percentage of blasts in bone marrow (BM) or peripheral blood (PB) with ≥ 20% blasts being a cut-off defining AML[4]. Due to the similar biology of higher risk MDS and AML, treatment options are comparable. Prognosis for both diseases is dismal, especially in patients who are not eligible for allogeneic hematopoietic stem cell transplant (allo-HSCT), the only curative treatment option.

The hypomethylating agent (HMA) 5-azacytidine ((AZA) has been approved for MDS in Europe and Australia based on the results of the MDS AZA-001 trial[5]. The overall response rate (ORR) ranges between 25% and 40%, and there is a significant reduction of the risk of progression to AML. A 7-day regimen of IV/SC AZA at 75 mg/m2 every 28 days demonstrated a 9.5 month OS benefit in patients with higher risk MDS based on IPSS in comparison with conventional care options[5–9]. Subsequent real-world data have nuanced these results with lower benefits of HMA compared with the original studies, which might be due to differences in adherence to dosing schedules, treatment duration, and less rigorous patient selection compared with the landmark clinical trials[10,11].

For patients progressing on HMA therapy, the prognosis is poor, with a median OS of 4-5.6 months for higher risk MDS patients[12,13] and there are very limited options for these patients, especially if they are not eligible for intensive chemotherapy or allo-HSCT.

Lately, the approval of the combination of AZA and venetoclax (VEN) has added benefits to the treatment of patients with HR MDS or AML not eligible for intense chemo or stem cell transplantation. The combination demonstrated improvements of response and survival rates especially in elderly or comorbid AML patients compared to single-agent AZA (CR/Cri of 66.4% vs. 28.3% and OS of 14.7 vs. 9.6 months)[14]. However, new and complementing treatment options in this vulnerable patient population not responding or relapsing are still urgently needed.

1.1.2 Telomeres and Telomerase

There is evidence that perturbations of telomere homeostasis are implicated in the pathogenesis of myeloid disorders, including MDS and AML[15]. Telomeres are structural elements of non-coding DNA acting as protective caps at the ends of chromosomes thereby preventing erosion of genomic DNA during cell division. Telomeres shorten with each round of cell division and specific mutations in telomere repair complex (TERT, TERC and associated proteins) can also lead to telomere attrition, eventually leading to replicative exhaustion and/or genomic instability. Proper telomere maintenance is of particular functional relevance in cellular compartments with high baseline cellular turnover such as the hematopoietic (stem cell) compartment. Telomere loss is prevented by the presence of the enzyme telomerase, which consists of 2 essential components: the human telomerase ribonucleic acid (RNA) template (hTR) and the human telomerase reverse transcriptase (hTERT) catalytic subunit. Telomerase counters telomere loss by the addition of TTAGGG repeats to the chromosome ends[16]. hTERT is overexpressed in MDS and AML[17,18] suggesting that targeting telomere length might be a valuable strategy to explore new treatment options in these two entities.

1.2 Imetelstat and rationale of the study

Imetelstat (GRN163L) is a covalently-lipidated 13-mer thiophosphoramidate oligonucleotide that acts as a potent specific inhibitor of telomerase. Telomerase inhibition leads to loss of a cancer cell's ability to maintain telomere length (TL), resulting in cell-cycle arrest, apoptosis, or senescence. Imetelstat binds with high affinity to the template region of the RNA component of hTERT and is a competitive inhibitor of telomerase enzymatic activity[19,20]. Treatment of various cancer cells with imetelstat in vitro increases their sensitivity to radiation, decreases their clonogenic potential, and results in altered expression of stem-cell related genes[21,22].

Data from a phase II study investigating imetelstat in lower risk MDS patients with red blood cell (RBC) transfusion dependency show 8- and 24-week RBC transfusion independency (TI) rates of 37% and 23%, respectively, with a median TI duration of 65 weeks in the overall population (n=57). In a subset population of HMA and lenalidomide-naïve patients, 8- and 24-week RBC TI rates were 42% and 29%, respectively, with a median TI duration of 86 weeks. Cytogenetic and mutational data revealed a reduction of the malignant clones, suggesting disease modification activity. These encouraging results in lower risk MDS provide an encouraging basis for further investigation of the agent in higher risk MDS and AML patients ineligible for allo-HSCT, constituting entities with an even greater need for new therapeutic options[23].

1.3 Risk benefit assessment

There are currently very few licensed drugs in the EU to treat MDS or AML patients having failed or being refractory to treatment with HMAs. Furthermore, allo-HSCT can be offered only to a minority of those patients. Therefore, new treatment options are urgently needed for this patient cohort.

Imetelstat, a first-in-class telomerase inhibitor, with its novel mechanism of action, may provide clinical benefit to MDS and AML patients. First clinical trial results suggest an activity in lower risk MDS and good tolerability[23]. The main side effects were thrombocytopenia and

neutropenia which were reversible in the majority of the patients. It is expected that this can be also managed effectively in the current patient population.

1.3.1 Justification for a protocol amendment

A decision was made to increase the initial frequency of dosing from once in [redacted] weeks to once in [redacted] weeks for at least the first [redacted] cycles [redacted] The justification for this is discussed also in section 7.6 [redacted].

[redacted] The most frequently recorded AEs were under the following Medical Dictionary for Regulatory Activities (MedDRA) system organ classes: infections and infestations, gastrointestinal disorders, general disorders and administration site conditions, and respiratory, thoracic and mediastinal disorders. This information is consistent with the safety profile of imetelstat according to the current version of the IB. A total of 30 SAEs were recorded in [redacted] patients, of which [redacted] were assessed as being at least possibly related to imetelstat. Of these [redacted] were assessed as unexpected and were reported as SUSARs. [redacted]

According to the safety data collected, no major change to the risk assessment was seen and there was no cause to conclude that imetelstat should not be used in patients with MDS/AML.

[redacted] Given the short half-life of imetelstat, there is reason to believe that an increased frequency of dosing may be beneficial to patients [redacted]

Given that no new safety signals to argue stopping imetelstat therapy were seen, the limited existence of treatment options and poor prognosis in this patient population, a decision was made to treat patients at a higher frequency of imetelstat administration for at least the first [redacted] cycles. There is a potential that neutropenia could be aggravated by the increased frequency of imetelstat. Therefore, the prophylactic use of antibiotics and antifungals has been recommended for use in patients according to local standards, especially when they are on the [redacted] dosing. This prophylactic use of antimicrobials may also prevent infections as a reason for disease progression.

A risk benefit assessment will be performed after enrolling some patients as described in section 4.2.

Additional note:

The ongoing COVID-19 pandemic may affect the conduct and continuity of this clinical trial and may require implementation of temporary or alternative safety-related procedures or mechanisms. A designated guideline describing this mechanism will be provided to the participating sites and is part of the site training procedures.

Participation in this trial does not create specific risks for patients apart from the general risks of the COVID-19 pandemic. The IMP can solely be administered intravenously, making it impossible to dose patients at home. Therefore, patients will need to come to the clinic or stay in the hospital for treatment and staging procedures. All possible efforts will be made to avoid exposure to SARS-CoV2 during these study visits and site staff contacts.

Deviations from protocol enrollment criteria due to COVID-19 are neither planned nor granted. Deviations from planned study procedures in response to COVID-19 have to be documented as being related to COVID-19. All temporary mechanisms utilized will remain in effect only for the duration of the pandemic.

2 Objective of the study and endpoints

2.1 Primary objective(s)

The primary objective of the study is to

- assess the efficacy of imetelstat for the treatment of AML and MDS patients failing or being refractory to hypomethylating agent (HMA)-based treatment

2.2 Secondary and other objectives

Secondary objectives of the study are to further assess efficacy and safety of imetelstat regarding following measures

- Toxicity as measured by NCI CTCAE v5.0
- Overall survival
- Progression-free-survival
- Duration of overall response
- Best overall response
- Quality of life (EORTC QLQ-C30)

2.3 Study endpoints

2.3.1 Primary endpoint

The primary endpoint of the study is defined as overall hematological response rate as assessed in [redacted] of treatment with imetelstat.

All patients with one of the following responses assessed by samples and procedures taken/carried out at [redacted] are defined as responders (assessed through the combined response criteria for MDS and AML used in this trial (see Appendix III a), section 16.3):

[1] CR, CRi, PR as defined in Appendix III a)

[2] Hematologic improvement (for one or several lines) as defined in Appendix III a)

Response rate is calculated as follows: number of responders divided by the number of all patients of the analysis set. Patients for whom the overall hematologic response cannot be determined will be considered as treatment failures.

2.3.2 **Secondary endpoints**

The following secondary endpoints will be analyzed in this study.

Safety Measurements

- Toxicity as measured by NCI CTCAE v5.0

Efficacy Measurements

- Overall survival
  - defined as the time from the beginning of imetelstat treatment until death or censored at the date of the last follow-up visit.
- Progression-free-survival
  - defined as the duration of time from time of imetelstat treatment to time of progression or death, whichever occurs first. A subject who has neither progressed nor died will be censored on the date of last follow-up visit.
- Duration of best overall response
  - measured from the time measurement criteria are met for CR, CRi, PR or SD (whichever is first recorded, defined in Appendix III a)) until the first date at which recurrent or progressive disease is objectively documented.
- Best overall response
  - defined as the best response recorded from the start of the imetelstat treatment until disease progression (taking as reference for progressive disease the smallest measurements recorded since the treatment started).
- Response based on IWG 2023 criteria[24] (MDS population only)
  - assessed in [redacted] of treatment with imetelstat as:
    - Overall Response Rate (ORR) = CR (or CR equivalent)* + PR + CR_L + CRh + HI, or
    - No response = Not meeting criteria for CR (or CR equivalent)*, PR, CR_L, CRh, or HI.
  - For definition see Appendix III b).
- Scores of EORTC QLQ-C30 (version 3)
  - Global health status / QoL
  - Functional scales
  - Symptom scales / items

3 Translational program

Bone marrow and blood samples will be obtained at the indicated time points and stored for translational analyses, in particular assessment of response and measurable residual disease and identification of prognostic or predictive biomarkers. If adequate BM aspirate is not attainable, peripheral blood may be used if at least 5% or more BM blasts are present. If this is not the case, a BM biopsy will be required.

3.1 Genetic profiling

Somatic mutation profiling will be performed at baseline, at visit V9 (assessment of primary end point) and at EOT, using targeted NGS assay at the central laboratories. Additional available time points may be analyzed if necessary.

3.2 Measurable residual disease (MRD)

Analyses of measurable residual disease, using a targeted NGS approach with unique molecular identifiers, will be performed at the Leipzig laboratory (for EU-based samples) or the QIMR Berghofer (for AUS-based samples) at visits V5, V9, and V13 for all informative patients.

3.3 Telomere length & telomerase profiling

Analyses of telomere length from mononuclear cells, will be performed using a ddPCR-based assay at the Leipzig laboratory (for EU-based samples) or the QIMR Berghofer (for AUS-based samples) at baseline, visit V9 (assessment of primary end point) and at EOT. Analyses of telomerase (hTERT) gene polymorphisms will be performed using targeted NGS at baseline.

3.4 Additional translational analyses

BM and PB samples will be stored in a study-specific biomaterial collection to enable subsequent hypothesis-driven translational analyses, including but not limited to whole-exome/genome sequencing, transcriptome sequencing, epigenetic profiling and single cell analyses.

In Australia, patients will have their tumor tissue sent for molecular screening, using the TSO-500 NGS panel and other molecular assays, to identify clinically actionable biomarkers in tumour tissue to be used to guide treatment, and predict response. Please refer to the country specific appendix for further details.

4 Organizational and administrative aspects of the study

4.1 Investigators and study sites

Please refer to IV Contacts and responsibilities.

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the center will be available in the center’s investigator site file (ISF) and the trial master file (TMF).

Requirements for investigators and study sites

The study site will be required to have an investigator with at least 2 years' experience in conducting clinical trials according to GCP as well as a substitute with comparable qualifications. The site must have a pool of suitable patients who can be recruited for the study.

All investigators must be qualified physicians. Each physician must supply his or her curriculum vitae (updated) for the TMF.

Investigators also must

- have special experience in the study indication and respective treatment as well as diagnostic procedures,
- have a GCP certificate,
- know main features of the local legal requirements,
- know the study protocol.

The investigator must sign the separate protocol signature sheet before subject recruitment may start. Likewise, all protocol amendments must be signed and dated by the investigator before coming into effect.

4.2 Data monitoring

From the additional [redacted] patients that are planned to be enrolled, a risk/benefit assessment is to be performed when [redacted] patients have started treatment, of which at least [redacted] patients have completed [redacted] full cycles of imetelstat (after [redacted]). This assessment will take into consideration available efficacy and safety data for these patients at that time. This data may include, for example, peripheral blast levels, WBC counts and details of AEs, SAEs and SUSARs collected in these patients. Bone marrow blast counts will also be included if available. The lead investigators in the study will analyse this data and perform the risk-benefit assessment, further details can be found in the study specific Safety Management Plan.

An independent data monitoring committee (DMC) will not be established for this study. It is deemed to not be mandatory as imetelstat has been tested in similar or more frequent dosages in previous studies and shown a generally well-tolerated and acceptable safety profile[23].

4.3 Financing

The study is financially supported by Geron Corporation.

5 Study design

5.1 Design overview

The present study is designed as a multicenter, open-label, single arm, prospective phase II study. Patients with AML or higher-risk MDS patients failing or being refractory to hypomethylating agent (HMA)-based treatment are eligible for the study. All study participants will receive the same IMP consisting of imetelstat. This section has been updated as part of a protocol amendment. Please see section 7.1.1 for details on the previous regimen and design.

Imetelstat sodium will be administered at a starting dose of [redacted] mg/kg given intravenously

every [redacted] weeks for [redacted] cycles of [redacted] days or until disease progression, unacceptable toxicity, withdrawal of consent, or lack of response. They will be assessed for response in cycle [redacted] according to the combined response assessment criteria for MDS and AML (Appendix III:). Non-responding patients will discontinue imetelstat treatment, undergo EOT and enter the follow-up phase of the trial. Patients who are categorized as responders based on at least PR (as described in section 2.3.1) and who have BM blasts ⩾5% at the response assessment in cycle [redacted] will continue to receive imetelstat every [redacted] weeks. Patients who are categorized as responders as per the primary endpoint definition and who have BM blasts <5% at the response assessment in cycle [redacted] will continue to receive imetelstat every [redacted] weeks. Treatment will continue until the subject experiences unacceptable toxicities or shows loss of response/disease progression per the combined disease assessment criteria used in this trial (see Appendix III a), section 16.3), withdraws consent, or meets any other discontinuation criteria defined in section 7.7.

The design is split into two phases. At first, it was planned to enroll [redacted] patients in the trial. According to the initial study design, if 1 or fewer responses were seen in these patients, the study should be stopped. [redacted], a decision was made to amend the frequency of imetelstat administration, at least for the first [redacted] cycles. An additional [redacted] patients are planned to be enrolled [redacted]. Please see section 1.3, section 7.6 [redacted] on the rationale for continuing the study and for the higher dosage justification.

Responding patients (defined as at least PR [partial remission]) are eligible to continue treatment until loss of response/disease progression.

The study will consist of a screening period, a primary treatment period (all patients), an extension treatment period (responders after 4 cycles of treatment only) and a posttreatment follow-up period. For the extension treatment period, in the absence of alternative treatment options, non-responders with stable or controlled disease may continue treatment at the investigator's discretion, in consultation with the sponsor, provided the disease remains controlled and none of the discontinuation criteria as described in section 7.7 are met.

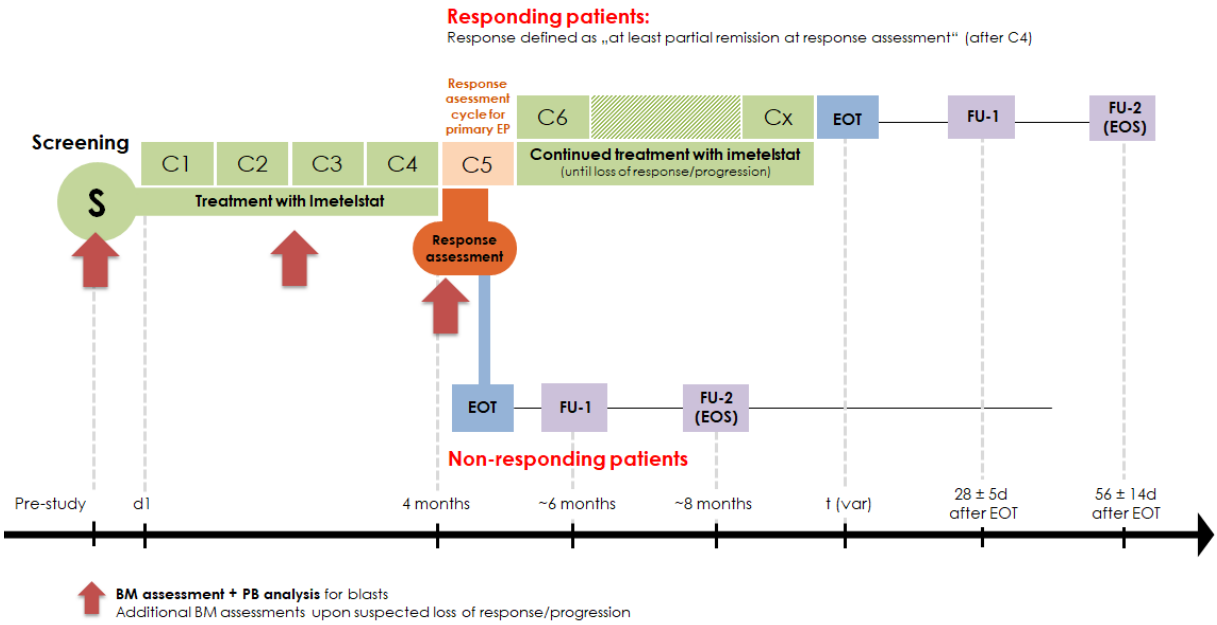
Patients who stop the study treatment for any cause will undergo an EOT visit at the latest 14 days after the decision of treatment discontinuation. The EOT visit will be followed by a first follow-up visit (FU1) 28 ± 5 days after EOT and a second FU visit = EOS visit approximately 2 months after EOT. FU2/EOS can be carried out on the phone and represents the last study visit for the patient.

The End of Study is considered at the time the last patient completed their evaluation 6 months after the end of the primary treatment period (in case of a continued responder) or following their follow-up period (in case of a non-responder). For avoidance of doubt, for non-responders with stable or controlled disease who continue treatment at the investigator's discretion, the end of study will be defined as the end of the follow-up period for said patient or discontinuation from the trial, whichever occurs later. The sponsor will ensure that subjects benefiting from treatment with imetelstat will be able to continue treatment for as long as the subject's disease is controlled, provided that an adequate stock of imetelstat is available.

A summary of the study design is given in Figure 1.

For detailed description of study visits and procedures see VII Schedule of assessments and procedures and section 8.2.

Figure 1: Study flowchart



5.1.1 Screening phase

Upon giving written informed consent, subjects will enter the screening phase to determine eligibility. Subject screening procedures will take place within 35 days prior to start of treatment. During the screening phase, the subject will undergo safety and other assessments to determine eligibility for the study.

Subjects must have at least 16 weeks of transfusion history available immediately preceding and including the date of the first administration of IMP in this study. Transfusion data should include the type of transfusion (e.g., RBC, platelets), number of units, and date of transfusion. RBC transfusion data should include the Hb value for which the transfusion was administered (i.e., pre-transfusion Hb value).

5.1.2 Primary phase of the treatment period ([redacted])

Imetelstat sodium will be administered at a dose of [redacted]. Subjects will receive imetelstat on day [redacted] of each [redacted] day treatment cycle. Also see VII Schedule of assessments and procedures (part 1).

Best supportive care (BSC) may be used in combination with imetelstat when clinically indicated per investigator. BSC includes, but is not limited to, treatment with transfusions, antibiotic, antiviral, and/or antifungal therapy as well as nutritional support as needed.

Subjects will receive imetelstat for at least the first [redacted] after the date of first dose, unless the subject experiences unacceptable toxicities, withdraws consent, or meets any other treatment discontinuation criteria as described in section 7.7.

5.1.3 Disease assessments in the primary phase of the treatment period ([redacted])

After cycles [redacted] and [redacted] (i.e., at the beginning of cycles [redacted] and [redacted]) response assessments will be carried out based on bone marrow and peripheral blood samples taken. For that, blood counts to assess potential cytopenias will be carried out and bone marrow and peripheral blood smears will be prepared to perform cytomorphology assessments.

Of these response assessments, the assessment at the end of [redacted] (performed at the beginning of cycle 5) is the primary endpoint (pEP) assessment.

Based on the outcome of the disease assessment in [redacted], if signs of disease progression are seen in the bone marrow, treatment with imetelstat will be stopped and the patient will undergo EOT and enter the follow-up phase.

Based on the outcome of the pEP ([redacted]) visit disease assessment, subjects will be either discontinued from treatment with imetelstat and enter the posttreatment follow-up phase (non-responders) or will continue treatment with imetelstat until loss of response/disease progression in the extension phase of the treatment period (responders) (see below at 5.1.4). In the absence of alternative treatment options, non-responders with stable or controlled disease may continue treatment in the extension phase at the investigator's discretion, in consultation with the sponsor, provided the disease remains controlled and none of the discontinuation criteria as described in section 7.7 are met. These subjects will follow the assessments and procedures according to the schedule of assessments for the extension phase (section VII, Part 2c). Responders who have BM blasts $\geqslant$5% at the response assessment in cycle [redacted] will continue to receive imetelstat every [redacted] weeks. Responders who have BM blasts <5% at the response assessment in cycle [redacted] will continue to receive imetelstat every [redacted] weeks.

The disease assessment will be performed according to combined response criteria based on IWG 2018 criteria (MDS)[1] and the criteria of the European LeukemiaNet (AML)[2] in order to harmonize the criteria for MDS and AML patients in this trial. The combined criteria are listed in Appendix III a), section 16.3.

- Evidence of clinical benefit is defined as:
    - **At least partial remission (PR)**:
        - This includes CR, CRi, PR and HI (any line) as per the combined response criteria used in this trial

All other assessment outcomes will result in treatment discontinuation. MLFS will be recorded but is not a criterion for treatment continuation. The corresponding patients (=non-responders) will then undergo the EOT visit and the follow-up period. As described above, in the absence of alternative treatment options, non-responders with stable or controlled disease may continue treatment in the extension phase at the investigator's discretion, in consultation with the sponsor. These subjects will follow the assessments and procedures according to the schedule of assessments for the extension phase (section VII, Part 2c).

Patients with at least PR at this pEP assessment will continue in the extension phase described below in section 5.1.4.

A risk/benefit assessment is to be performed when [redacted] patients have started treatment, of which at least [redacted] patients have completed [redacted] full cycles of imetelstat ([redacted]). Please refer to section 4.2 for more details.

5.1.4 Extension phase of the treatment period (from [redacted]1 on)

Subjects who meet the criteria to remain on treatment after completion of the [redacted] disease assessment and have BM blasts ⩾5% may continue dosing on day [redacted] of each [redacted] treatment cycle in the extension phase of the treatment period. Subjects who meet the criteria to remain on treatment but have BM blasts <5%, may continue dosing on day [redacted] (only) of each [redacted] treatment cycle in the extension phase of the treatment period.

Treatment will continue until the subject experiences unacceptable toxicities or shows loss of response/disease progression per the combined disease assessment criteria used in this trial (see Appendix III a), section 16.3), withdraws consent, or meets any other discontinuation criteria defined in section 7.7.

For subjects who continue treatment in the extension phase of the treatment period, each disease assessment should confirm continued clinical benefit and absence of disease progression per the combined disease assessment criteria. For patients exhibiting a response to treatment, each disease assessment will also determine the frequency of imetelstat treatment (once in [redacted] weeks or once in [redacted] weeks) based on BM blast levels. Serial measurements of safety and efficacy will be continued on scheduled study visits (see VII Schedule of assessments and procedures [part 2]) in the extension phase of the treatment period. BSC may be continued to be used in combination with imetelstat when clinically indicated per investigator. All subjects who receive at least one dose of imetelstat will undergo end of treatment (EOT) evaluations when imetelstat is discontinued. The reason for discontinuation will be recorded.

Non-responders with stable or controlled disease may continue treatment in the extension phase of the study at the investigator's discretion as described in section 5.1.3. For these subjects, safety and efficacy data may be collected, without impacting the primary study objectives, timelines, or statistical analyses. These subjects will follow the assessments and procedures according to the schedule of assessments for the extension phase (section VII, Part 2c).

5.1.5 Posttreatment follow-up (FU) period

All AEs will be recorded by the investigator from the time the subject signed the ICF until [redacted] days after the last dose of IMP. Additionally, all serious AEs (SAEs) made known to the investigator at any time thereafter and are suspected of being related to imetelstat will also be documented. Therefore, at [redacted] days the first FU visit will take place. For the second FU visit (=EOS) please refer to VII Schedule of assessments and procedures (part 3).

5.2 End of the clinical study

For this study, the primary outcome will be analyzed after the last patient has completed the study (individual EOS). The end of the study as a whole will be the date when the clean database is available and ready for export for the statistical analyses. However, the primary completion event of the study will be the date of last patient end of study (LPEOS).

5.3 Closure of study sites/premature termination of the clinical study

The sponsor might close this study or parts thereof at any time if

- risk-benefit ratio becomes unacceptable based on safety findings or any interim analysis from this study or upcoming information from other clinical or animal studies
- the study conduct does not suggest a proper completion of the study within a reasonable time frame

The investigator has the right to close his/her center at any time.

All closures should occur only after consultation between sponsor, CPI and study center(s). All affected institutions (e.g., IEC(s), competent authorities, study center) must be informed as applicable according to local law. All study materials (except documentation and research samples taken for correlative studies that have to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.

6 Study population

6.1 Justification of selection criteria

The selection criteria are chosen to ensure that subjects with specific risks for administration of the IMP and / or subjects with conditions which may have an impact on the objectives of the study are excluded.

6.2 Justification of gender selection

Male and female subjects will be included in the present study representing the population of patients suffering from AML / HR MDS without any gender prevalence.

6.3 Inclusion criteria

Subjects must fulfill all of the following criteria before inclusion in the study:

1 Signed written informed consent
2 Male and female ≥ 18 years at the first screening
3 Must be able to adhere to the study visit schedule and other protocol requirements
4 Initial diagnosis of AML or MDS according to WHO 2016 classification
5 At least one cytopenia (ANC < [redacted]/µL or platelet count < [redacted]/µL or hemoglobin < [redacted] g/dL)
6 a. Failure to achieve complete or partial response or hematological improvement observed after at least six azacitidine monotherapy or four decitabine monotherapy based 4-week treatment cycles administered during the past two years
OR
b. Failure to achieve complete or partial response or hematological improvement observed after at least two 4-week treatment cycles with azacitidine plus venetoclax or with decitabine plus venetoclax during the past two years

OR

c. Relapse after initial complete or partial response or hematological improvement observed after at least six (azacitidine) or four (decitabine) based 4-week treatment cycles administered during the past two years
OR

d. Relapse after initial complete or partial response or hematological improvement observed after at least two 4-week treatment cycles with azacitidine plus venetoclax or with decitabine plus venetoclax during the past two years
OR

e. Intolerance to treatment with HMA-based therapy during the past two years

7 Not eligible for allogeneic stem cell transplantation

8 ≥ 5% bone marrow blasts at screening

9 Off all other treatments for AML/MDS for at least 14 days; G-CSF and erythropoietin are allowed before and during the study as clinically indicated

10 ECOG performance status of 0-2

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

[redacted]

12 Availability of blood counts and transfusion events for previous 16 weeks

13 Women of childbearing potential and practicing a highly effective method of birth control according to the Clinical Trial Facilitation Coordination Group Recommendation (Version 1.1, 2020):

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - o oral
  - o intravaginal
  - o transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - o oral
  - o injectable
  - o implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

For females, these restrictions apply for 3 months after the end of dosing. Note: If the childbearing potential changes after start of the study (e.g., woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) a woman must begin a highly effective method of birth control, as described above

14 A woman of childbearing potential must have a negative serum (ß-human chorionic gonadotropin [ß-hCG] or urine pregnancy test at screening and agree to be tested on day 1 of every cycle and at EOT

15 A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study. For males, these restrictions apply for 3 months after the end of dosing
16 France-specific inclusion criterion: Subjects participating at French sites must be covered by the French public welfare system.
17 Patients who are relapsed or refractory to, or not eligible for, therapy with approved and available FLT3 or IDH1/IDH2 inhibitors or other approved targeted therapies.

6.4 Exclusion criteria

Subjects are to be excluded from the study if they display any of the following criteria:

1 Chemotherapy within the 14 days prior to the first dose of imetelstat being administered (other than hydroxyurea)
2 Subject has known allergies, hypersensitivity, or intolerance to imetelstat or its excipients (refer to the IB)
3 Subject has received an experimental or investigational drug or used an invasive investigational medical device within 30 days prior to day 1 of C1
4 Prior treatment with imetelstat
5 Prior history of intensive chemotherapy or hematopoietic stem cell transplant
6 Major surgery within 4 weeks prior to day 1 of C1 (excluding the placement of vascular access and other minor surgical procedures)
7 Diagnosed or treated for malignancy other than MDS or AML, except:
   a. Malignancy treated with curative intent and with no known active disease present for 3 years before day 1 of C1
   b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   c. Adequately treated cervical carcinoma in situ without evidence of disease
8 Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of day 1 of C1, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification
9 Known history of human immunodeficiency virus (HIV) or any uncontrolled active systemic infection requiring IV antibiotics
10 Active systemic hepatitis infection requiring treatment (carriers of hepatitis virus are permitted to enter the study), or known acute or chronic liver disease including cirrhosis
11 Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator’s opinion, could compromise the subject’s safety, interfere with the imetelstat metabolism, or put the study outcomes at undue risk; Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

12 Females who are pregnant or are currently breastfeeding or planning to become pregnant while enrolled in this study or within 3 months after the end of dosing
13 Subject is a man who plans to father a child while enrolled in this study or within 3 months after the end of dosing
14 Subject is in custody by order of an authority or a court of law

15 Previous assignment to treatment during this study
16 Close affiliation with the investigator (e.g., a close relative) or persons working at the study site
17 Subject is an employee of the sponsor or involved CRO
18 Criteria which in the opinion of the investigator preclude participation for scientific reasons, for reasons of compliance, or for reasons of the subject's safety

6.5 Subject registration and identification

After signing the ICF (=start of screening period), each subject has to be registered in the eCRF by the trial site personnel and will then automatically assigned a patient number. The patient number is a unique, 12-digit number consisting of a three-digit study identification code, a two-digit country code with a two-digit number identifying the trial site followed by a three-digit number in ascending order, e.g.:

IME-DE01-001

This number will be used throughout the entire study to identify the study participants.

6.6 Screening failures and drop-outs

A subject who terminates the study for any reason (e.g., failure to satisfy the selection criteria) before first treatment with IMP is regarded as "screening failure".

A subject who discontinues study treatment prematurely for any reason is defined as "dropout" if the subject has already received study medication.

In all cases, the reason for study discontinuation must be recorded in the eCRF and in the subject's medical records.

For all subjects determined as screening failures the following information is to be captured in the subject´s source documents and eCRF page(s): the date informed consent form (ICF) was signed, demographics, the reason subject did not qualify for the study, and the investigator´s signature for the eCRF pages.

Details for premature discontinuation of study treatment are given in section 7.7.

Details for the premature termination of the whole study or study parts are provided in section 5.3.

Subjects who prematurely discontinue participation before end of treatment will not be replaced. Screening failures will be replaced.

7 Investigational Medicinal Product (IMP) Imetelstat

7.1 Treatment regimen

During the primary and extension treatment phase all subjects will receive the same IMP (imetelstat) as outlined below.

Imetelstat will be administered as an intravenous (IV) infusion every [redacted] to subjects by the study staff at the clinical site and administration is to be documented in the subject's source record.

Imetelstat will be provided by Geron and will be administered as a 2-hour IV infusion (± 10 minutes) at a constant rate using an infusion pump. The baseline weight (i.e., body weight determined at Screening) will be used to calculate the dose of imetelstat sodium to the nearest 0.1 mg. The dose should be recalculated if there is a ≥ 10% weight change from baseline. Note that the total dose may be recalculated more frequently (eg, at each study visit) depending on local practice. Imetelstat will be administered IV on a [redacted] cycle.

The first dose of imetelstat should be administered within 72 hours of enrollment.

All subjects will receive a starting dose of [redacted]. All subjects will be treated for at least [redacted] cycles, followed by a response assessment according to combined response criteria based on IWG 2018 criteria (MDS)[1] and the criteria of the European LeukemiaNet (AML)[2] (see Appendix III a), section 16.3). Subjects exhibiting a response and have BM blasts ⩾5% at the time of the response assessment after [redacted] treatment cycles will continue to receive imetelstat every [redacted] weeks until loss of response/disease progression. Patients who are categorized as responders and have BM blasts <5% at the response assessment will continue to receive imetelstat every [redacted] weeks until loss of response/disease progression. For patients exhibiting a response to treatment, each disease assessment after cycle [redacted] will also determine the frequency of imetelstat treatment ([redacted]) based on BM blast levels. Non-responding patients at the time of the response assessment after 4 treatment cycles will discontinue imetelstat treatment, undergo EOT and enter the follow-up phase of the trial. In the absence of alternative treatment options, non-responders with stable or controlled disease may continue treatment at the investigator's discretion, in consultation with the sponsor, provided the disease remains controlled and none of the discontinuation criteria as described in section 7.7 are met. These subjects will follow the assessments and procedures according to the schedule of assessments for the extension phase (section VII, Part 2c).

If signs of disease progression are present in bone marrow after [redacted] doses with imetelstat (at the early disease assessment in [redacted]), treatment with imetelstat must be discontinued and the patient undergoes EOT.

Imetelstat dose delay or reduction for Grade 3 or Grade 4 toxicity will be instituted as needed, per the instructions provided in Table 1, Table 2, Table, 3, and Table 4. Note that these instructions are intended for Grade 3 or Grade 4 toxicities observed at the time of the next planned dose. These instructions are not applicable when toxicities occur between doses and subsequently resolve to Grade <3 by the time of the next planned dose.

Imetelstat may be held for up to 28 days from the expected start date of the scheduled cycle; a hold >28 days must be reviewed and approved by the sponsor. Imetelstat should be discontinued permanently if it cannot be restarted within 28 days due to toxicity. If the subject

is exhibiting an otherwise positive clinical response to treatment and the toxicity appears to be manageable, contact the sponsor to discuss the specific case before study drug is discontinued.

7.1.1 Treatment regimen prior to amendment to protocol version 5.0

[redacted] a decision was made to update the treatment regimen.

The initial design involved all subjects receiving a starting dose of [redacted] mg/kg of imetelstat sodium given IV [redacted]. After [redacted] cycles of treatment, all subjects would undergo a response assessment according to the combined response criteria based on IWG 2018 criteria (MDS) and the criteria of the European LeukemiaNet (AML) as described in Appendix III: a). Subjects with at least a partial remission according to this criteria (PR, CR or CRi) would continue to be treated with imetelstat until loss of response/disease progression at which point they would undergo EOT and enter the follow-up phase of the trial. Non-responding patients at this response assessment would undergo EOT and enter the follow-up phase of the trial.

7.2 Properties of Imetelstat

7.2.1 Clinical Pharmacology of Imetelstat

Pharmacokinetics showed dose dependent increases in exposure within the [redacted] Pharmacokinetics of imetelstat was characterized by a rapid initial decline of plasma concentration at the end of the infusion, which presumably reflects the distribution phase with half-life ranging from 4 to 5 hours. The excretion and metabolism of imetelstat has not been evaluated in the clinical setting. However, it is anticipated that, similar to other oligonucleotides, imetelstat is predominantly metabolized in the tissue through nuclease–mediated cleavage of nucleotide residues from the parent oligonucleotide and excreted mainly via the urinary tract.

7.2.2 Clinical Safety of Imetelstat

A total of [redacted] subjects with various solid tumors and hematologic disorders were treated with imetelstat, either as monotherapy or in combination with other anticancer agents across 12 completed studies. In all completed studies so far, imetelstat has overall an acceptable safety profile when administered as a monotherapy or in combination with chemotherapies to subjects with hematologic malignancies or solid tumors. Observed toxicities were manageable through a combination of dose delays and dose modification. These comprised [redacted] subjects who participated in monotherapy studies and [redacted] subjects who participated in combination therapy studies.

A detailed summary of safety is provided in the current Investigator's Brochure (IB). At the time of writing this protocol, this was edition 19[25].

In the following, a summary on the safety of imetelstat as monotherapy in especially the

hematologic setting is provided, as this is of relevance for the present trial.

7.2.2.1 Safety of Imetelstat as Monotherapy in Hematologic Malignancies

Cytopenias, particularly thrombocytopenia and neutropenia, are the primary dose limiting toxicities (DLTs) identified with imetelstat. The frequency and severity of all cytopenias, particularly thrombocytopenia and neutropenia, are associated with the imetelstat dose intensity (actual dose and frequency of dosing); however, cytopenias are manageable through dose modifications, reversable and of short duration, and with limited clinical consequences, for example febrile neutropenia.

Completed Monotherapy Studies in Hematologic Diseases

[redacted]

Ongoing Study 63935937/MDS3001 (NCT02598661) in Low- or Intermediate-1 Risk MDS

Treatment with imetelstat was generally well tolerated and consistent with the existing safety profile. The most common TEAEs (cytopenias) were predictable and manageable, and for the majority of events in Part 1 these were reversible.

[redacted]

For complete safety information on imetelstat please refer to current Investigator's Brochure provided in the context of this protocol.

7.3 Dose modification guidelines

Imetelstat sodium dose modifications will be performed as described in *Table 1*. All dose modifications must be recorded in the eCRF.

Table 1: [redacted]

Titration	Dose regimen

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

7.3.1 **Dose Modifications for Hematologic Toxicities**

For any occurrence of [redacted]

It is recommended to contact the sponsor before discontinuing treatment due to [redacted]

7.3.2 **Dose Modifications for Non-hematologic Toxicities, Excluding Hepatic Toxicities**

The actions in *Table 2* should be taken for Grade 3 or 4 non-hematologic/non-hepatic toxicities present at the planned start of a dosing cycle. [redacted]

Table 2: Dose Modifications for Grade 3 and 4 Non hematologic/Non-hepatic Toxicities

Occurrence	Action
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

7.3.3 **Dose Modifications for Hepatic Toxicities**

[redacted]

Table 3: [redacted]

Adverse event	Action to be taken
[redacted]	[redacted]
[redacted]	[redacted]
[redacted] *Subjects with Grade 2 bilirubin at study entry should have worsening bilirubin with concomitant Grade 2 AST or ALT elevation	[redacted]

[a] Extensive investigation includes repeating liver enzyme and serum bilirubin tests with fractionation once or twice weekly until levels return to baseline. Obtain additional tests to evaluate liver function, as appropriate (i.e., INR, albumin). In addition, obtain a detailed history of symptoms, prior or concomitant disease, concomitant medications (including nonprescription herbal and dietary supplements), alcohol use, recreational drug use, special diets and environmental chemical agents. The following should be ruled out: acute viral hepatitis types A, B, C, D and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease and may require gastroenterology and hepatology consultations. Consider hepatology (or gastroenterology) consultation.

7.3.4 Dose Modifications for COVID-19 Symptoms or Positivity (any Grade)

- Closely monitor for clinical signs and symptoms of COVID-19 (eg, fever, cough, shortness of breath, breathing difficulties). For more comprehensive overview on signs and symptoms please refer to guidance from the WHO and regional health authority guidance.
- For subjects on treatment who have clinical signs and symptoms, if possible, perform COVID-19 testing according to local recommendations to assess COVID-19 status. Study treatment must be held for patients who meet any of the following:
    - have confirmed COVID-19 infection based on testing
    - have clinical signs and symptoms consistent with COVID-19 infection in the absence of testing
    - do not have clinical signs and symptoms consistent with COVID-19 infection but have been exposed to a person with confirmed COVID-19 infection based on testing
- Study treatment can resume only after the subject has tested negative for COVID-19 according to local guidelines or, if testing was not performed, is asymptomatic (eg, no fever, no cough, no shortness of breath, no breathing difficulties) for at least 14 days.
- Cases of confirmed, suspected, or exposed COVID-19 infection leading to changes in study conduct should be documented in the eCRF, as applicable.

7.4 Infusion-Related Reactions

All subjects receiving an infusion of study drug must be premedicated with diphenhydramine (25 to 50 mg) and hydrocortisone (100 to 200 mg), or equivalent. It is recommended that subjects are monitored for at least 1 hour after the infusion has been completed.

[redacted]

Table 4: Management of Infusion-Related Reactions

Occurrence	Action
[redacted]	[redacted]

7.5 Drug logistics and accountability

After trial site approval/initiation and as needed thereafter, imetelstat will be shipped to a responsible person at the local pharmacy or directly to a responsible person at the trial site. The Sponsor or a delegate is responsible for quality control, labelling, batch release, batch recalls, packaging and shipment to the study sites.

The local pharmacy/study site is responsible for accounting, ordering and reconstitution of imetelstat and handing over to investigator or designee, if applicable.

The administration of imetelstat will be done by a member of the investigator's team. This person will ascertain and document that the subject receives the treatment as planned.

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. The study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a

hospital/clinic pharmacist. The study drug will be supplied only to subjects participating in the study and in accordance with this protocol. The study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at any site other than the study sites agreed upon with the sponsor.

The study drug must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. All study drugs will be stored and disposed of according to the sponsor's instructions. The study site personnel must not combine contents of the study drug containers.

Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. Reshipment of unused study drug to the distributor must be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form. Potentially hazardous materials such as used ampules, needles, syringes, and vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records on site.

Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor study file; the site-relevant elements of this information will be available in the ISF. The responsible site personnel will confirm the receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol.

Details of storage, handling and administration of imetelstat are described in the IMP Manual.

7.6 Selection of doses in the study

Exposure-response analyses and benefit/risk evaluations performed for part 1 of MDS3001 demonstrate that imetelstat sodium [redacted] mg/kg every [redacted] weeks is well tolerated and provides adequate [redacted], it was decided to increase the frequency of dosing from once in [redacted] weeks to once in [redacted] weeks for the first [redacted] cycles. At the assessment in cycle [redacted], if the patient is responding to treatment but has BM blasts $\geqslant$ 5%, they will continue to receive imetelstat every [redacted] weeks until loss of response/disease progression. If the patient is responding to treatment and has BM blasts <5%, they will continue to receive imetelstat every [redacted] weeks until loss of response/disease progression. For these patients exhibiting a response to treatment, each further disease assessment will also determine the frequency of imetelstat treatment (once in [redacted]) based on BM blast levels. Patients who are not responding to treatment by cycle

[redacted] will discontinue imetelstat treatment, undergo EOT and enter the follow-up phase of the trial. Given the short half-life of imetelstat and the poor prognosis for this patient population, this initial increase in the frequency of imetelstat treatment may be more effective for a population of high-risk MDS and AML patients than the regimen used for patients with lower risk MDS.

The study MYF2001 was performed in patients with myelofibrosis where imetelstat was administered every [redacted] weeks at either [redacted] or [redacted] mg/kg. The safety data collected from this study with more frequent dosing than in study MDS3001 also demonstrated that treatment with imetelstat every [redacted] weeks was also generally well tolerated and consistent with the existing safety profile.

7.7 Treatment discontinuation

All subjects will have an End of Treatment (EOT) visit at the time of imetelstat discontinuation. All subjects who received at least one dose of imetelstat will be followed for 3 months post last dose of imetelstat.

The following events are considered sufficient reasons for discontinuing a subject from treatment with the IMP:

- Lack of efficacy
- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- Pregnancy
- Protocol violation
- Study terminated by Sponsor
- Disease Progression as per combined response criteria based on IWG 2018 criteria (MDS)[1] and the criteria of the European LeukemiaNet (AML)[2]
- Other (to be specified on the eCRF)

The reason for discontinuation of treatment should be recorded in the eCRF and in the source documents. The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the investigator may contact the sponsor and forward appropriate pseudonymized supporting documents for review and discussion.

Subjects who discontinue from treatment for any reason will enter the follow-up period (for details refer to section VII Schedule of assessments and procedures and section 5.1.5 Posttreatment follow-up (FU) period.

7.8 Overdose

There are no available data on imetelstat overdose.

7.9 Prestudy and concomitant medication

7.9.1 Prestudy therapy

Prestudy therapies administered up to 35 days before day 1 of cycle 1 as well as any

transfusions received before day 1 of cycle 1 must be recorded at screening.

7.9.2 Premedication

All subjects must be premedicated before imetelstat administration to decrease the risk and severity of infusion reactions. Premedication with an antihistamine (diphenhydramine 25 to 50 mg or equivalent) and a corticosteroid (hydrocortisone 100 to 200 mg or equivalent) are recommended. The medicinal product used as premedication are authorised and they are used in accordance with the terms of their marketing authorisations. [redacted]

7.9.3 Concomitant medications

[redacted]

The following [redacted]

[redacted]

Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a subject into the study. Concomitant therapies should be recorded beyond 30 days only in conjunction with new or worsening adverse events or serious adverse events that meet the criteria outlined in Section 9.1.3, Serious Adverse Events.

7.9.4 Drug-drug Interactions

Imetelstat has a low potential for clinically relevant DDIs with major CYP450 enzymes and drug transporters. Imetelstat is not an inhibitor or inducer of CYP450 enzymes or an inhibitor of the P-gp, BCRP, BSEP, OAT3, OCT1, OCT2, MATE1, or MATE2-K transporters in vitro. Imetelstat is a potential inhibitor of the OATP1B1, OATP1B3, and OAT1 transporters, and the UGT1A1 enzyme in vitro; however, considering its short plasma half-life and lack of plasma accumulation with an every 2 to 4-week dosing regimen, clinical drug interactions of imetelstat with substrates for these transporters and enzymes is unlikely[25]. Nonetheless, consider caution when co-administering imetelstat with drugs that are known to be affected by these transporters and enzymes.

7.10 Post-study therapy

After conclusion of the clinical study, patients will receive further medical care as per standard of care and local institution guidelines at the discretion of the treating physician.

8 Procedures and variables

8.1 Description of visits

Any questions regarding the protocol should be directed to the National Coordinating Investigator or the Sponsor´s Medical Expert.

All of the protocol required assessments are listed in VII Schedule of assessments and procedures.

All data obtained from these assessments must be recorded in the subject's source documentation. All study visits during the Treatment Period (both primary and extension phases) must occur within 3 days of the scheduled day.

A 5-day window is allowed for the EOT visit. If a subject is discontinued during a regular scheduled visit, all EOT procedures should be completed at that visit.

A window of ± 5 days is allowed for posttreatment FU 1 visit at which the last AE assessment will take place. The subsequent FU 2 visit (=EOS) will take place within ± 14 days of the scheduled date as described in VII Schedule of assessments and procedures.

Serum chemistry laboratory analyses, automated CBC, cytomorphology and cytogenetic analyses will all be performed locally.

Cytomorphology analyses will be carried out locally.

Refer to the eCRF completion guidelines for additional information related to data entry requirements of local laboratories.

Sample collection, processing, storage, and shipment procedures (for translational NGS analyses and study-specific biomaterial collection) will be provided in the Study Laboratory Manual.

8.1.1 Screening ([redacted])

A subject information session will be held. Considering site-specific logistic requirements, the investigator may decide upon timing of the screening examinations (e.g., starting immediately

after the informed consent procedure at the earliest; possible split-up into more than one visit). If the (first) screening procedures already start on the same day (same date) as the subject signs the informed consent form, the time of the subject's signature must be recorded in the source documents.

Note: No screening procedures may be performed unless written informed consent has been obtained.

Assessment of inclusion/exclusion criteria for study eligibility

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within [redacted]) of the first administration of the IMP (refer to VII Schedule of assessments and procedures for further information). Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

Procedures and evaluations to be performed during the screening period are specified in VII Schedule of assessments and procedures and in section 8.2 Descriptions of assessments.

Bone marrow and peripheral blood samples for local assessments

MDS/AML diagnosis confirmation at screening requires both BM, and PB samples. Samples will be reviewed locally.

The screening BM, and PB samples should be collected within the protocol screening window or [redacted] prior to the first administration of the IMP. If a subject is rescreened (e.g., due to retesting of another lab), repeat BM samples do not need to be collected contingent the initial samples were adequate for cytomorphology/cytogenetic assessment.

Sample collection, processing and storage should be done as per local standard procedures.

Local cytomorphology assessment

BM and PB samples will be prepared and reviewed locally for analysis to confirm MDS/AML diagnosis and baseline blast percentages as well as WHO classification (Appendix I, section 16.1)) prior to the first administration of the IMP.

Local cytogenetic analysis

Local laboratories will conduct cytogenetic analysis. The local laboratory will provide standardized analysis and reporting for all subjects.

In case a historic record of cytogenetic for the subject (not older than 3 months) is available, these results can be used for the screening visit. But at the latest at [redacted]) a new analysis must be performed.

Results from local cytogenetic analysis should be used to determine baseline IPSS-R category for MDS patients (Appendix II, section 16.2).

8.1.2 Enrollment for treatment

Patients eligible for study participation will be enrolled by confirmation in the eCRF. Therefore, all assessments between screening and cycle 1 day 1 must be available to check the eligibility criteria. With enrollment, the previously assigned patient number will be used further. For details, please refer to section 6.5.

8.1.3 Treatment period

The subject will start treatment upon confirmation of eligibility. The subject must start treatment within [redacted] of signing the ICF. If screening assessments are performed within 72 hours of C1D1, serum chemistry laboratory assessments and physical examinations need not be repeated at C1D1 with the exception of automated CBC.

If subject completed the QoL EORTC QLQ-C30 questionnaire at Screening within 2 weeks of C1D1, it does not have to be repeated at C1D1. If performed on C1D1, it should be completed prior to IMP administration.

On dosing days, local laboratory levels should be assessed prior to each IMP administration to ensure dose modification rules are followed as outlined in section 7.3 Dose modification guidelines.

8.1.4 Primary Phase of the Treatment Period: [redacted]

Subjects will receive IMP on [redacted] each [redacted] treatment cycle.

Treatment cycles are [redacted] in duration and will occur as described in section 7.1 Treatment regimen.

After completion of cycle 2, early disease assessments according to the combined MDS/AML response criteria (Appendix III a), section 16.3) will be performed, involving local cytomorphology assessment. If signs of disease progression are present at this assessment, treatment with imetelstat must be discontinued and the patient undergoes EOT.

Procedures/evaluations to be performed during the Primary Phase of the Treatment Period and their frequency are specified in VII Schedule of assessments and procedures and in section 8.2. Descriptions of assessments. The procedures/evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

8.1.5 MDS/AML disease assessment: [redacted]

The primary MDS/AML disease assessment according to the combined MDS/AML response criteria (Appendix III a), section 16.3) (primary endpoint assessment) will be performed on samples taken at [redacted]. The assessment will be performed by the corresponding investigator.

The disease assessment for the primary endpoint should be completed after four completed cycles with imetelstat (allowing for dose delays). For the disease assessment at least the results of the cytomorphology assessment, automated CBC values and cytogenetic results of visit 9 as well as any information on Hb and transfusions between enrollment and visit 9 are required and must be available prior to / for the disease assessment.

In order for subjects to remain on treatment beyond the first four cycles, the following criteria must be confirmed upon the completion of the disease assessment by the investigator based on the combined response criteria based on IWG 2018 criteria (MDS)[1] and the criteria of the European LeukemiaNet (AML)[2]:

- **At least partial remission (PR)**:
    - This includes CR, CRi, and PR and HI (any line) as per the combined response criteria used in this trial (see Appendix III a))

MLFS will be recorded but is not a criterion for treatment continuation.

Based on the outcome of the disease assessment, subjects will either be discontinued from treatment with IMP and enter the post-treatment follow-up period or continue treatment with IMP in the extension phase of the treatment period.

For subjects that meet the criteria to continue treatment in the extension phase, the duration between the last dose of IMP administered in the primary phase and the first extension phase dose should not be delayed solely due to awaiting cytomorphology/cytogenetics results contingent that the investigator has confirmed absence of signs of disease progression based on review of peripheral blood parameters.

A BM biopsy is to be collected only when adequate aspirate is not attainable or if the BM aspirate shows fewer than 5% bone marrow blasts. Whenever a BM sample is collected, both BM and PB smears are to be prepared. Refer to the Laboratory Manual for additional information.

Further procedures/evaluations to be performed at [redacted] are specified in VII Schedule of assessments and procedures, part 1 and in section 8.2 Descriptions of assessments.

8.1.6 Extension Phase of the Treatment Period: [redacted]

Subjects who meet the criteria to remain on treatment after completion of the [redacted] disease assessment and have BM blasts ⩾5% may continue dosing on [redacted] of each [redacted] treatment cycle in the extension phase of the treatment period. Subjects who meet the criteria to remain on treatment after completion of the [redacted] disease assessment and have BM blasts <5% may continue dosing on [redacted] (only) of each [redacted] treatment cycle in the extension phase of the treatment period.

Treatment will continue until the subject experiences unacceptable toxicities, disease progression per the combined response criteria used in this trial (Appendix III, section 16.3), withdraws consent, or meets any other discontinuation criteria (section 7.7).

BM and PB samples will be collected (e.g., for cytomorphology, cytogenetic analysis) and the disease assessment will be repeated by the investigator at [redacted] and at [redacted] in the extension phase. Patients showing a benefit from the therapy in [redacted] can continue treatment with the IMP. Beyond [redacted], disease assessments (including cytomorphology and therefore collection of BM and PB samples) will be carried out every 3 months and at every timepoint of suspected progression starting [redacted] after the last disease assessment in [redacted]. Also see VII Schedule of assessments and procedures, part 2).

Each BM assessment [redacted] months thereafter) should also be used to determine the frequency of treatment with imetelstat until the next disease assessment: every [redacted] weeks (if BM blasts are ⩾5%) or every [redacted] weeks (if BM blasts are <5%).

A BM biopsy is to be collected only when adequate aspirate is not attainable or if the BM aspirate shows fewer than 5% bone marrow blasts. Whenever a BM sample is collected, both BM and PB smears are to be prepared for the cytomorphology assessment. Refer to the Laboratory Manual for additional information.

In addition, information related to all transfusions received during the treatment period (including those received outside the trial site) should be available prior to completion of each

disease assessment.

For subjects to continue treatment in the extension phase of the treatment period, each disease assessment should confirm continued clinical benefit and absence of disease progression per the combined criteria used in this trial (Appendix III).

Additional procedures/assessments as outlined in section 8.2 will also continue in the extension phase. The frequency of procedures/assessments in the extension phase may differ from the primary phase. Refer to VII Schedule of assessments and procedures, part 2 for additional information related to required assessments/procedures and frequency in the extension phase.

For non-responders with stable or controlled disease in the absence of alternative treatment options, who continue treatment in the extension phase as described in section 5.1.3, safety and efficacy data may be collected, without impacting the primary study objectives, timelines, or statistical analyses. These subjects will follow the assessments and procedures according to the schedule of assessments for the extension phase (section VII, Part 2c).

8.1.7 Dose delays

In case of dosing delays, the visit schedule will be adjusted. Visits indicating dosing will only be performed if the patient is ready to receive their next dose. These visits will be postponed in case of dosing delays (section 7.3). Visits without dosing of subjects (for example [redacted] in responding patients with <5% BM blasts) should be performed two (2) weeks ±3d after the preceding dosing visit irrespective of dosing delays.

During the time period of dose delay, the following assessments/procedures should be performed:

- If dose delay is due to a laboratory or vital signs abnormality, the assessment that was the reason for the dose delay should be repeated at least on weekly basis.
- If dose delay is due to an AE, perform hematology and serum chemistry at least every 2 weeks thereafter and before next dose administration.

8.1.8 Unscheduled visits

Should it become necessary to repeat an evaluation (e.g., laboratory tests or vital signs), the results of the repeat evaluation should be entered as an additional unscheduled visit in the eCRF.

Refer to the eCRF completion guidelines for detailed instructions related to eCRF data entry.

8.1.9 End of Treatment Visit

An EOT evaluation will be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made. Evaluations will be performed as specified in VII Schedule of assessments and procedures, part 3.

If a subject is discontinued during a regular scheduled visit, all EOT procedures should be completed at that visit. If a procedure had been performed within [redacted] of the EOT visit, it

does not need to be repeated unless clinically indicated per investigator discretion.

BM sample collection should only be performed at EOT visit if [redacted] from prior BM procedure.

The reason for discontinuation will be recorded in the eCRF and in the source document for all subjects, regardless of whether they are dosed or not. Reasons for treatment discontinuation are provided in section 7.7.

8.1.10 Post-treatment Follow-up Period

All subjects discontinued from protocol-prescribed therapy for any reason will be followed for a period of [redacted] days after the last dose of IMP for AE reporting, as well as serious adverse events (SAEs) made known to the Investigator at any time thereafter that are suspected of being related to the IMP (FU1).

Beyond FU1, all subjects discontinued from protocol-prescribed therapy for any reason should be followed for state of condition/survival until the end of the follow-up period (refer to VII Schedule of assessments and procedures, part 3).

Females of child-bearing potential (FCBP) should avoid becoming pregnant for [redacted] after the last dose of IMP and male subjects should avoid fathering a child for [redacted] after the last dose of IMP.

Data regarding subsequent MDS/AML therapies and other malignancies/pre-malignancies as well as date and cause of death, if applicable, will be recorded in the eCRF. The investigator must make every effort to obtain information regarding the subject´s survival status before determining the subject is lost to follow-up. If the subject is discontinued from follow-up, the reason for discontinuation should be recorded in the eCRF at EOS.

Follow-up may be conducted by telephone contact with the subject, family, or the subject´s treating physician.

8.2 Descriptions of assessments

8.2.1 Study entry and general assessments

8.2.1.1 Physical examinations and vital signs

This will include: general appearance, vital signs, height (measured at screening only), weight (at screening and on study drug dosing days only), seated blood pressure, temperature, heart rate, and respiratory rate. Significant findings must be included on the appropriate eCRF. Refer to VII Schedule of assessments and procedures for timing of physical examinations during the study.

8.2.1.2 Demography and medical history

The subject´s date of birth and sex will be recorded on the appropriate eCRF. Relevant medical history (including recent surgical history) and current medical conditions, including symptoms related to MDS/AML, must also be recorded on the appropriate eCRF at Screening.

Presence of history of MDS/AML disease and other prior malignancies will also be recorded on the appropriate eCRF.

8.2.1.3 Prior therapies

Prior transfusion history

Transfusion history must be available for at least the 16 weeks immediately preceding and including the date of the first IMP administration. Transfusion data should include the type of transfusion (e.g., RBC, platelets), number of units, reason and date of transfusion.

Transfusion data should also include the pretransfusion Hb levels that triggered the RBC transfusions. For platelet transfusions, data should include the platelet value for which the platelet transfusion was administered.

All RBC transfusion events during the 16 weeks immediately preceding and including the date of first administration of the IMP should be recorded (including any transfusions at outside local institutions). RBC transfusions administered for elective surgery will not be relevant for meeting RBC transfusion inclusion criteria requirements, but should still be recorded in the eCRF.

The RBC transfusion data during the 16 weeks immediately preceding the first administration of IMP will be used to determine the baseline RBC transfusion requirement (necessary for HI-E assessment) for an individual study subject.

As mentioned above (in 8.2.1.2), prior AML/MDS specific treatments will be recorded. The following information will be captured:

- type of HMA (azacitidine or decitabine)
- number of total HMA cycles received
- best response with HMA according to IWG (MDS) / ELN (AML) criteria
- number of cycles until best response
- duration of response

8.2.2 Investigational Medicinal Product

For treatment regimen, dose modification rules and treatment discontinuation please refer to sections 7.1, 7.3 and 7.7, respectively.

8.2.3 Safety assessments

The safety measures assessed are routinely used in clinical studies evaluating the safety of IMP for hematologic malignancies. Safety assessments, including (but not limited to) physical examination, vital signs, ECG, hematology, serum chemistry, pregnancy testing (for FCBP subjects only), AEs, concomitant medications and procedures, and transfusion data collection and assessment, will be performed at the frequency specified in VII Schedule of assessments and procedures.

8.2.3.1 Eastern Cooperative Oncology Group Performance Status (ECOG PS)

Performance status will be assessed by the investigator during Screening and at [redacted]) indicated at VII Schedule of assessments and procedures using ECOG criteria provided in Appendix IV, section 16.4.

8.2.3.2 Pregnancy test and counseling

This protocol defines an FCBP as a sexually mature woman who: 1) has not undergone a

hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

A medically supervised serum pregnancy test (conducted locally) is to be obtained and verified negative in all FCBPs at screening. The investigator will appraise a female subject as an FCBP according to this definition. Justification must be recorded in the eCRF and the source document. Pregnancy testing is not required for non-FCBP subjects.

Serum beta human chorionic gonadotropin (β-hCG) pregnancy test (which must be negative) with a minimum sensitivity of 25 mIU/mL will be performed within 5 weeks prior to first administration of IMP. Urine (or serum) pregnancy test will be performed to assess subject eligibility within 72 hours prior to the first administration of IMP, if the initial serum pregnancy test did not already occur within 72 hours of dosing (negative results required for IMP administration).

During the Treatment Period urine or serum pregnancy test is allowed.

For males and FCBP, counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at the beginning of each treatment cycle or monthly (e.g., in the event of dose delays).

Refer to VII Schedule of assessments and procedures for timing of pregnancy testing and counseling during the study.

8.2.3.3 Adverse events

Please refer to section 9.

8.2.3.4 Prior and concomitant medication/procedures

All prior/concomitant MDS/AML specific medications taken in the 35 days prior to first study drug administration will be recorded on the appropriate eCRF(s).

All prior/concomitant procedures within the 8 weeks prior to first study drug administration will be recorded on the appropriate eCRF(s).

Relevant prior anti-cancer treatments related to MDS/AML should be recorded on the appropriate eCRF(s) regardless of treatment discontinuation/procedure date.

8.2.3.5 Serum chemistry

Serum chemistry (e.g., sodium, potassium, chloride, bicarbonate [if available], calcium, magnesium, phosphorus, blood urea nitrogen [BUN], creatinine, creatinine clearance and/or estimated glomerular filtration rate, glucose, albumin, total protein, alkaline phosphatase, total bilirubin (direct/indirect bilirubin only if total bilirubin is elevated), AST/SGOT or ALT/SGPT, lactate dehydrogenase [LDH], uric acid) will be analyzed by the local laboratory. Hepatitis panel is to be considered at screening if liver enzymes are elevated.

Refer to section VII Schedule of assessments and procedures for timing of serum chemistry assessments during the study.

8.2.3.6 ECG

An ECG is to be performed at screening.

8.2.4 Efficacy assessments

Treatment response will be assessed locally by the investigator in accordance with the combined response criteria used for this trial (see Appendix III, section 16.3) cytomorphology assessment, transfusion assessment, hematology laboratory parameters and cytogenetic analysis.

BM aspiration (or biopsy, if adequate aspirate is not attainable or if the BM aspirate shows fewer than 5% bone marrow blasts) samples for assessing treatment response will be collected at the frequency specified in section VII Schedule of assessments and procedures. Whenever a BM sample is collected, a PB smear is to be prepared. PB smears are also prepared on visits each cycle every [redacted] weeks.

Cytogenetic testing is to be completed whenever a BM sample is obtained for assessment of cytogenetic response. BM biopsy can be used for cytogenetic testing if adequate aspirate is not attainable or if the BM aspirate shows fewer than 5% bone marrow blasts (note that specific handling of the biopsy is required for cytogenetics testing).

8.2.4.1 Hematology

Hematology assessment (e.g., red blood cell [RBC] count, complete blood count [CBC], white blood cell [WBC] with differential, hemoglobin, hematocrit, nucleated red blood cells [nRBC], absolute reticulocyte count, platelet count, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], and red blood cell distribution width [RDW]) will be tested by the local laboratory.

Refer to section VII Schedule of assessments and procedures for timing of hematology assessments during the study.

Also, all Hb levels available for the 16 weeks preceding the first IMP administration will be collected in the eCRF for subsequent HI-E assessment.

8.2.4.2 Transfusion data collection and assessment

All transfusions received in a time window of 16 weeks preceding the first IMP administration will be collected in the eCRF for subsequent HI assessments.

During the study, all received transfusions will be collected in the eCRF.

For transfusions, the following should be documented:

- type of transfusion (e.g., pRBC or platelet)
- number of units
- reason for transfusion
- date of transfusion
- Hb value for which any RBC transfusion is given (i.e., pretransfusion Hb)
- platelet value for which any platelet transfusion is given

Clinical site staff should confirm if any transfusions were received by the subject (including any at outside local institutions in between study visits) prior to each IMP administration via use of patient diary or other local procedure in place at the investigational site.

8.2.4.3 MDS / AML disease assessment

Disease assessment will be done according to the combined response criteria stated in Appendix III, section 16.3.

During the course of the study, whenever a BM sample is collected, a PB smear is to be prepared as well.

Sample collection, processing and storage will be provided in the study's Laboratory Manual.

Refer to section VII Schedule of assessments and procedures for timing of sample collection during the study.

8.2.5 Quality of life

Patient-reported QoL will be measured by using the EORTC QLQ-C30 questionnaire (version 3).

Refer to section VII Schedule of assessments and procedures for timing of QoL data collection.

8.2.6 Follow-up assessments

8.2.6.1 Posttreatment MDS therapy and survival

Long-Term Posttreatment Follow-up for OS and data collection for subsequent MDS therapies may be conducted by record review (including public records if allowed by local regulations) and/or telephone contact with the subject, family, or the subject´s treating physician. The investigator must make every effort to obtain information regarding the subject´s survival status before determining the subject is lost to follow-up.

8.3 Central laboratories for translational analyses and biomaterial collection

8.3.1 Europe: Laboratory [redacted]

For biomarker analyses and study-specific biomaterial collection, additional samples of BM and PB must be prepared and sent by the site to the corresponding lab specified below. Samples should be sent overnight within 24 hours at ambient conditions. The following samples must be taken at Screening [redacted] and subsequently for responders at [redacted] and at the EOT visit if this visit occurs more than 90 days from the last time a BM aspiration was carried out.

- 10 ml sodium heparinized (Na-Hep) peripheral blood
- 5 ml sodium heparinized (Na-Hep) bone marrow

Sample collection, processing and storage, and shipment procedures will be provided in the study's Laboratory Manual.

Shipping address for Germany and France:

[redacted]

Shipping address for Australia:

The process used in these central laboratories is no general biobanking, but analyses and storage of samples will be done for the purpose of this study only.

9 Safety

9.1 Definitions of adverse events and adverse drug reactions

9.1.1 Adverse events (AE)

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE.

In the following differentiation between medical history and AEs, the term “condition” may include abnormal e.g., physical examination findings, symptoms, diseases, or laboratory or ECG test results.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present at the time of signing of informed consent are recorded as medical history.
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history.
- Conditions that started or worsened after signing of informed consent will be documented as adverse events.
- The term “disease progression” should be avoided when recording AEs. It is preferred that the diagnosis/signs/symptoms are used as the reported terms. Disease progression can be captured by the investigator as the alternative causality for the event.
- Instead of the term “infusion related reaction”, the signs and symptoms of the reaction should be captured to be able to characterize the event.

9.1.2 Treatment emergent adverse events (TEAE)

A treatment emergent adverse event (TEAE) is an adverse event that occurs only once

treatment with IMP has started or is an already present event that worsens either in intensity, frequency during or following the treatment or changed from being not suspected to being suspected following the treatment.

9.1.3 Serious adverse events (SAEs)

A serious adverse event (SAE) is classified as any untoward medical occurrence that at any dose (including overdose) meets the following seriousness criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization*
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Important medical events that may not result in death, be life- threatening, or require hospitalization, or results in disability, may be considered serious based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Medical and scientific judgment should be exercised every time in deciding whether such an AE should be considered serious.

9.1.4 Adverse drug reactions (ADR) and serious adverse drug reactions (SADR)

An adverse drug reaction (ADR) is any noxious and unintended response to an IMP related to any dose with at least a reasonably possible causal relationship to the IMP. Accordingly, a serious adverse drug reaction (SADR) meets at least one of the seriousness criteria as mentioned above. Events assessed as having no causal relationship to the IMP are considered AEs/SAEs.

9.1.5 Suspected unexpected serious adverse reactions (SUSAR)

A suspected unexpected serious adverse reaction (SUSAR) is an adverse event which is regarded as serious, is suspected to have at least a possible causal relationship with the IMP and whose nature or severity is not consistent with the product information available for the IMP.

9.1.6 Adverse events of special interest (AESI)

The occurrence of new malignancies such as secondary primary malignancies (SPM) will be monitored as events of special interest and shall always be considered as SAEs. SPMs shall be reported regardless of the product administrated to the study subject.

Events of new malignancy, pre-malignant lesions (excluding benign tumors or benign neoplasia) are to be reported to the Sponsor´s designated Safety Department within 24 hours of the Investigator’s knowledge of the event by facsimile, or other appropriate method, using the provided SAE Report Form. All SAE criteria (e.g., hospitalization) should be marked if applicable, and all events must be marked as an “Important Medical Event” even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject’s source documents. Documentation related to the diagnosis of malignancy must be provided at the time of reporting as an SAE (e.g., any confirmatory histology or

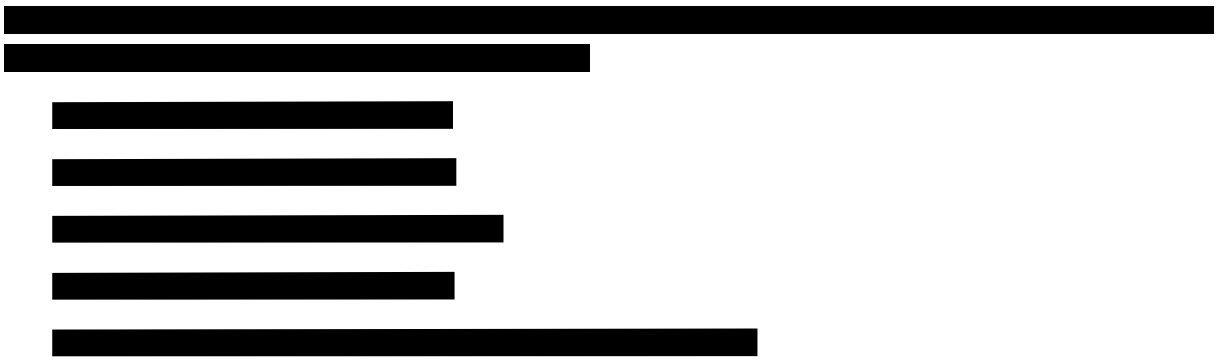
cytology results, X- rays, CT scans, etc.).

Malignancies or cancerous tumors are lesions capable of invading into adjacent tissues and may be capable of spreading to distant tissues. A benign tumor has none of those properties.

Malignancy or cancer is characterized by anaplasia, invasiveness, and metastasis.

Premalignant or precancerous lesions refer to a state of disordered morphology of cells that is associated with an increased risk of cancer. If left untreated, these conditions may lead to cancer. Such conditions are usually either dysplasia or benign neoplasia (and the dividing line between those is sometimes blurry). Sometimes the term “precancer” is used to describe carcinoma in situ, which is a noninvasive cancer that has not progressed to an aggressive, invasive stage. Not all carcinoma in situ will progress to invasive disease.

Premalignant lesions are morphologically atypical tissue which appears abnormal under microscopic examination, and in which cancer is more likely to occur than in its apparently normal counterpart.



9.2 Classification of AEs

9.2.1 Severity

The Common Terminology Criteria for Adverse Events (CTCAE) is used by default as severity grading scale AEs in cancer therapy, clinical trials, and other oncology settings. A grading (severity) scale is provided for each AE term. All appropriate treatment areas have access to a copy of the CTCAE current Version 5.0 in the investigator site file or as an electronic document provided by the sponsor (see Appendix VI, section 16.6). All serious adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the IMP, and the patient’s outcome in a separate SAE-document. The investigator must evaluate each adverse event for its seriousness and for its relationship to the IMP.

9.2.2 Seriousness

The following guidelines will be used to describe seriousness.

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect
- medical important event

Hospitalization is a seriousness criterion. The following admission to hospitals should not be recorded and reported as an SAE:

- Hospital admission due to administrative reasons
- Hospital admission prior to signing the ICF
- Hospital admission not associated with a worsening of a preexisting condition
- Hospital admission without an AE, e.g. elective hospitalization and surgery for treatment of the underlying AML/MDS disease including transfusions

9.2.3 Relationship to IMP

All AEs and SAEs must have their relationship to IMP assessed by the investigator who examines and evaluates the study participant based on temporal relationship and clinical judgment. The degree of certainty about causality will be graded using the categories below:

Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to IMP administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the IMP (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure, if necessary.

Probable Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the IMP, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possible Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the IMP). However, other factors may have contributed to the event (e.g., the study participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to IMP administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the IMP) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not Related – The AE is completely independent of IMP administration, and/ or evidence exists that the event is related to another etiology. There must be an alternative, definitive etiology documented by the investigator.

9.2.4 Expectedness of IMP

The sponsor will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information (most current version of IB) previously described for the

IMP.

9.3 Documentation and reporting of AE/SAE

All subjects will be monitored for AEs during the study by the study personnel. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

The investigator must assess all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the event´s outcome. All laboratory values have to be signed by the investigator.

For adverse events reporting the medical diagnosis must be reported. In case the diagnosis is not available, individual symptoms can be reported to fulfill reporting timelines. If a diagnosis becomes available at a later stage, it must be added to the reported event. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome. The Investigator shall make every effort to obtain a copy of the autopsy report and or death certificate and transmit this, after anonymization, to the sponsor.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

All AEs (for example observed AEs, AEs mentioned upon open questioning by a member of the investigator's team or spontaneously reported AEs by the subject) will be recorded by the Investigator from the time the subject signs informed consent until 28 (± 5) days after the EOT visit (i.e. TEAEs) as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IMP (i.e. SADRs).

If the AE onset is prior to the first dose of IMP and the event does not increase in severity after initiation of IMP, the AE is then considered to be a pre-treatment AE and will not be reported in the TEAE incidence tables.

If the onset is prior to the first dose of IMP and the severity increases thereafter, the event is documented as a TEAE.

If the onset is after the first dose of IMP, the event is documented as a TEAE. This rule is consistent with the treatment-emergent signs and symptoms convention for counting AEs.

An exception will be if a patient experiences an SAE after signing informed consent but prior to receiving a study drug. In this case, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol-required procedure.

The sponsor ensures that all persons involved in the treatment of study subjects are adequately informed about the responsibilities and actions required when AEs occur. Study subjects will be asked at each visit whether they have experienced AEs or SAEs. AEs will be documented in the study subject's medical records and in the (e)CRF.

The investigator is responsible for evaluating all AEs to determine whether seriousness criteria as defined in section 9.1.2 are met. AEs observed, mentioned upon open questioning by a

member of the investigator's team or spontaneously reported by the subject will be documented. In case of ongoing AEs after the last follow-up visit – especially when related to treatment with the IMP – the respective AE will be followed until resolution, if possible.

Important follow-up information should also be reported to the Sponsor when available. If relevant information is missing at the time of the initial SAE report, the reporter should provide it in follow-up SAE report(s). A follow-up report should contain new, updated or corrected information. The follow-up report should describe whether the event has resolved or continues, if and how it was treated including documentation of all supportive actions taken.

9.3.1 Events not to be treated as AEs

- Preplanned interventions or occurrence of endpoints specified in the study protocol are not considered AEs, if not defined otherwise (e.g. as a result of overdose)
- Medical or surgical procedures, e.g., surgery, endoscopy, tooth extraction, transfusion that are not associated with the indication under study. However, the event leading to the procedure is considered an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition prior to the screening visit that does not worsen
- Situations in which an adverse event change did not occur. In addition, the following reasons for hospitalizations are not considered AEs, and therefore not SAEs:
  - Hospitalizations for cosmetic elective surgery, social and/or convenience reasons. Treatment, which were elective or pre-planned, treatments for a pre-existing condition that is unrelated to the indication under study and did not worsen.
  - Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris
  - Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., elective hip replacement for arthritis
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Admission to a hospital or other institution for general care, not associated with any deterioration in condition; or treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious and not resulting in hospital admission

9.3.2 Events not to be treated as SAEs

Due to the seriousness of the disease in this study, certain conditions defined as SAEs will be excluded from expedited reporting on a SAE report form.

- Elective hospitalization and surgery for treatment of the underlying disease including transfusions
- Elective hospitalization to simplify treatment or study procedures

- Events that are only and unequivocally caused by progression of the underlying disease, except transformation to AML which is always to be reported as an SAE

Primary disease progression and related SAEs, e.g., hospitalization for surgery/diagnostic procedures, except for life-threatening status or death caused by the underlying malignant disease will not be considered and reported as SAEs if they are unrelated to study medication according to the investigator. The assessment of relationship to study medication must also be documented.

Further information on safety reporting can be found in the study specific Safety Management Plan.

9.4 Investigator reporting responsibilities

The investigator must keep copies of all AE information, including correspondence with the sponsor and the EC/IRB, on file. The investigator will be responsible for notifying regulatory bodies and ECs/CECs/IRBs as locally required.

The Investigator is obligated to report any SAE/pregnancy to the Sponsor within **24 hours** of becoming aware of the event to ensure the safety of all participants in the study and to meet regulatory reporting requirements. Although all information required for completion of an SAE report form may not be available within the specified time period, an initial report should be submitted with the available information. Any new information obtained about the serious adverse event must be added to the existing eCRF form.

The investigators report all occurring events electronically by completing the designated page in the eCRF system. A backup paper report form is provided to all sites as well. In case the eCRF cannot be accessed for any reasons, the SAE should be reported by completing and signing the paper backup form. The signed form will then be sent to:

Address: [redacted]

Phone: [redacted]

Fax: [redacted]

Email: [redacted]

Information on the form must be transferred to the eCRF by the site when it is accessible again. Each SAE and pregnancy must be followed up until resolution or stabilization by submission of updated reports (FU-report) to the designated recipient.

9.5 Sponsors reporting responsibilities

In accordance with Clinical Trial Regulation 536/2014 the sponsor should promptly notify all concerned investigators, institutions and the regulatory authorities of SUSARs and all findings that could affect adversely the safety of subjects, impact the conduct of the study or alter IEC/authority approval to continue the study. The sponsor will inform all trial sites about reported relevant changes of the benefit-risk ratio (e.g., occurrence of SUSARs) according to all applicable regulations.

Reporting of SUSAR by the Sponsor to the European Eudravigilance database (Article 42 CTR

536/2014)

Sponsor of a clinical trial performed in at least one European member state shall report electronically and without delay to the Eudravigilance database all relevant information about the following SUSARs:

a) all SUSARs from this clinical trial, irrespective of its location (site in the European Union or in a third country);

b) all SUSAR related to the same active substance, regardless of pharmaceutical form and strength or indication investigated, in investigational medicinal products used in the clinical trial, occurring in a clinical trial performed exclusively in a third country, if that clinical trial is sponsored: by that sponsor, or by another sponsor who is either part of the same parent company as the sponsor of the clinical trial, or who develops a medicinal product jointly, on the basis of a formal agreement, with the sponsor of the clinical trial;

c) all SUSARs to investigational medicinal products occurring in any of the subjects of the clinical trial, which are identified by or come to the attention of the sponsor after the end of the clinical trial.

The period for the reporting of SUSAR depends on the seriousness of the reaction:

- in the case of fatal or life-threatening SUSAR, as soon as possible and in any event not later than 7 days after the sponsor became aware of the reaction. If the initial report is incomplete, the sponsor shall submit a completed report based on the initial information within an additional 8 days;
- in the case of non-fatal or non-life-threatening SUSAR, not later than 15 days after the sponsor became aware of the reaction;
- in the case of a SUSAR which was initially considered to be non-fatal or non- life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than 7 days after the sponsor became aware of the reaction being fatal or life-threatening;
- If significant new information on an already reported case is received by the sponsor, this information shall be reported as a follow-up report within 15 days.

More specifics about how safety reporting will be carried out in all participating countries is defined in the Safety Management Plan and safety agreements and contracts.

9.6 Development Safety Update Report (DSUR)

Once a year, the sponsor will supply a report on the safety of study subjects – development safety update report - in accordance with ICH E2F and ICH GCP with all relevant information during the reference period to the competent authority and the responsible ethics committee.

The date of the first approval of the study by a competent authority is the reference date for the start of the year which the annual safety report covers. Data lock point will be the last day of this year. The sponsor will supply the report within 60 days after the data lock point.

Further details will be given in the study-specific Safety Management Plan.

9.7 Reporting of serious breaches

The sponsor must report serious breaches of the EU Regulation 536/2014 or of the protocol (the version that is valid at the time of the breach) no later than seven days of awareness of the breach. Wherever a serious breach is suspected by the investigator, this must be reported to the sponsor within 24 hours to:

Email: [redacted]

A serious breach is defined as a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

10 Statistical methods and sample size calculation

The analytical methods presented below summarize the more complete plans to be detailed in a separate document in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. A statistical analysis plan (SAP) must be written and finalized before database closure and statistical analysis for the interim analysis. The SAP must provide full details of the analyses, the data displays, and the algorithms to be used for data derivations.

10.1 General statistical considerations

No confirmatory statistical analysis will be conducted due to the changes described in section 5 and section 7.1. All analysis will be only explorative.

Statistical analysis will be performed using SAS® version 9.4 or higher.

Summary statistics (arithmetic mean, standard deviation, median, minimum, and maximum for quantitative variables) will be presented by the treatment group. Frequency tables for categorical data will be provided. Medical history findings will be summarized using MedDRA terms.

Missing values will not be imputed. Outliers will be identified prior to the analyses of the efficacy endpoints and have to be checked by the study physician. According to the decision of the data management, the statistician and the study physician, outliers will be kept in the database or set to “missing”.

10.2 Analysis sets

10.2.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all patients who received at least one dose of study drug and fulfilled the inclusion criteria. The FAS is the primary dataset for analysis.

10.2.2 Per Protocol Set (PPS)

The Per Protocol Set (PPS) will be defined as the subset of patients of the FAS that reached study [redacted] and who have no major protocol deviations as to be determined on a per-subject basis immediately before data base lock.

10.2.3 Safety Evaluation Set (SES)

Safety summaries will be based on the Safety Evaluation Set, which will consist of all patients who received at least one dose of study drug.

10.3 Sample size calculation

The study was designed as single-arm phase II trial. The design of the trial focused on demonstrating that the efficacy is greater than an undesired level of efficacy (p_0) which would indicate that the treatment is ineffective. A Simon's two-stage design was used to allow for initial assessment of efficacy. The sample size calculation was based on the following assumptions.

- Given Null hypothesis H_0: $p \leq p_0$
- Alternative hypothesis H_1: $p > p_0$
- Level of inefficacy $p_0 = 0.05$
- Expected true response rate $p_1 = 0.2$
- Type-1-error $\alpha = 0.05$, one-sided
- Type-2-error ß = 0.1

The null hypothesis that the true response rate is 0.05 was planned to be tested against a one-sided alternative. In the first stage, [redacted] patients were accrued. If there were 1 or fewer responses in these [redacted] patients, the study should be stopped. Otherwise, it was planned to accrue [redacted] additional patients for a total of [redacted] The null hypothesis would be rejected in favor of the alternative hypothesis if 5 or more responses are observed in [redacted] patients. This design yielded a one-sided type I error rate of no more than 0.05 and power of at least 0.9 when the true response rate is 0.2. To account for a loss of follow up of ~10%, enrollment of up to [redacted] patients is expected. Similarly, a total of [redacted] patients were planned to be enrolled prior to the interim analysis to ensure [redacted] evaluable patients for the interim analysis.

[redacted] Due to potential benefits for the patients, the study will continue in an exploratory approach with change dose frequency as described in section 7.1.

10.4 Randomization / Stratification

This is an open-label, single-arm trial. Therefore, randomization and blinding techniques are not applicable.

10.5 Subject disposition

An accounting of study patients by disposition will be tabulated in each analysis population by treatment regimen (once in a [redacted] cycle for at least [redacted] cycles vs. [redacted] in a [redacted] (once every [redacted] days) for at least [redacted] cycles). A patient flow chart will be provided including the following information:

Number of subjects

- screened,
- screen failure,
- enrolled,
- treated,

- discontinued (along with primary reason for discontinuation) including primary treatment phase and extension phase,
- completed.

A summary of subjects enrolled by site will be provided. Protocol deviations will be listed.

10.6 Patient characteristics

Age, height, weight, BMI, gender, race and baseline hematology parameters will be summarized in a descriptive manner. The sum of transfusions required during the 16 weeks immediately preceding the first IMP administration and descriptive statistics for the sum will be calculated. Medical history data will be summarized using frequency tabulations by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Frequency tables of MDS classification according to WHO will be shown.

Previous and concomitant medications will be coded according to the WHO drug code and the Anatomical Therapeutic Chemical (ATC) Classification System. They will be summarized by type (e.g., previous, concomitant) by tabulating the number and percentages of patients.

Patient characteristics will be displayed by treatment regimen and overall.

10.7 Treatment compliance

The dose administered at each cycle for the treatment agent will be assessed and dose intensity will be summarized by treatment regimen. Details will be provided in the SAP.

10.8 Efficacy analysis

Definitions of primary and secondary endpoints are specified in section 2.3. Due to the change in treatment regimen, efficacy analysis will be done separated by treatment regimen.

10.8.1 Analysis of primary endpoint

The absolute and relative frequencies of overall hematological response as assessed in [redacted] of treatment with imetelstat will be evaluated using the FAS and repeated for the PPS. Treatment success will be determined by patients showing at least PR (CR, CRi or PR) and/or showing a hematologic improvement for one or several lines.

According to the previous design (see section 10.3), an absolute cut-off value was used to determine the study outcome at the interim and final analysis. Due to the changes described in section 5 and 7.1, the primary endpoint will only be analyzed in an exploratory way.

Summary statistics and an exact two-sided 90% confidence interval for overall hematological response rate using the Clopper-Pearson method will be presented.

10.8.2 Analysis of secondary endpoints

Secondary efficacy measurements include overall survival (OS), progression-free survival (PFS), time to treatment failure, duration of response, best overall response and response analysis based on the IWG 2023 criteria (for MDS population only). Moreover, Health-Related Quality of life will be evaluated using EORTC QLQ-C30 (version 3). Analyses of secondary endpoints will be performed in exploratory manners based on the FAS and separated by treatment regimen.

10.8.2.1 Overall survival

Overall Survival (OS) will be assessed using Kaplan-Meier method. The death of patient is regarded as the event of interest. The estimates obtained are invariably expressed in graphical form. Median survival time, the survival rate at week [redacted]) and more additional timepoints (defined in SAP) with two-sided 95% confidence intervals (CI) using the complementary log-log transformation method will be tabulated.

10.8.2.2 Progression-free-survival

Kaplan-Meier method will be used to assess progression-free survival (PFS). Kaplan-Meier Curves depicting PFS will be generated. Additionally, median PFS, PFS rate at week [redacted]) and more additional timepoints (defined in SAP) of treatment with imetelstat will be reported. The two-sided 95% confidence intervals (CI) for the median, week [redacted], and week [redacted] will be calculated using the complementary log-log transformation method. Detailed methodology is provided in the SAP.

10.8.2.3 Duration of response

Median time and 95% confidence interval for duration of response will be summarized using descriptive methods.

10.8.2.4 Best overall response

Best overall response at the end of treatment will be summarized. The summary table will include counts and percentages for each response category (CR, PR, SD etc. described in Appendix III, section 16.3).

10.8.2.5 Response based on IWG 2023

Response based on the updated IWG 2023 criteria at visit 9 will be analyzed only for MDS population. Absolute and relative frequencies will be provided for each category.

10.8.2.6 HRQoL

Health-Related Quality of Life (HRQoL) will be accessed using EORTC QLQ-C30, version 3. The raw score for global health status / QoL, functional scales and symptom scales / items will be summarized with descriptive statistics by visit. Moreover, the convert score will also be provided, more details will be described in the SAP.

10.8.3 Analysis of other efficacy variables

Transfusion data collected in eCRF will be analyzed using descriptive statistics by visits.
More details will be provided in SAP.

10.9 Safety analysis

All safety analyses will be performed on the SES. At least summary statistics and, where meaningful, change from baseline will be reported. Full details will be included in the SAP. Safety analysis will be performed by treatment regimen and overall.

10.9.1 Toxicity analysis

Toxicity will be summarized during the study. Details will be provided in the SAP.

10.9.2 Extent of Exposure

Duration of treatment, total dose and dose intensity will be summarized. Dose modifications will also be summarized if applicable. Details will be provided in the SAP.

10.9.3 Adverse Events

Adverse events will be defined as treatment-emergent if they are newly occurring or worsen following treatment with imetelstat. For this trial, the only adverse events that will be counted will be TEAEs (see section 9.1.2). TEAEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

Tables for TEAEs will show the number and frequencies of incidences by severity and relation to IMP. Individual listings of AEs, SAEs and deaths within 30 days from last exposure to IMP will be generated.

TEAEs leading to premature discontinuation of study drug or withdrawal from the study will be summarized and listed in the same manner.

The percentage of patients with unacceptable toxicity acc. to CTCAE v5.0 criteria will be provided for week 4 (C4) and week 17 (beginning of C5, V9), and accompanying exact two-sided 95% confidence interval using the Clopper-Pearson method will be provided.

10.9.4 Clinical laboratory results

Clinical chemistry and vital signs will be summarized descriptively for the original data as well as for the difference to baseline. Patients with laboratory values outside of the normal reference range at any postbaseline assessment will be listed.

10.10 Subgroup analyses

Additional subgroup analyses of exploratory nature may be defined in the SAP.

10.11 Interim analysis

[redacted]

10.12 Analysis and reporting

Data will be analyzed and the report prepared after the last subject has completed the study (LPEOS). This is defined as the time the last patient completed their evaluation 6 months after the end of the primary treatment period (in case of a continued responder) or following their follow-up period (in case of a non-responder). For avoidance of doubt, for non-responders with stable or controlled disease who continue treatment at the investigator's discretion, the end of study will be defined as the end of the follow-up period for said patient or discontinuation from the trial, whichever occurs later. The sponsor will ensure that subjects benefiting from treatment with imetelstat will be able to continue treatment for as long as the subject's disease is controlled, provided that an adequate stock of imetelstat is available. Data associated with the continued treatment of patients will be collected outside the scope of this trial. The statistical analysis report (SAR) will be prepared after completion and correction of all case report forms (database lock).

11 Documentation

All data relevant to this study are to be documented by the responsible investigator in an (e)CRF immediately after measurement has been taken. Entering data may be delegated to members of the study team but the investigator will have to check and sign the (e)CRF entries. All paper-based documentation should be completed legibly, in black or blue ink. If it is necessary to make corrections, a single line should be drawn through the original entry, the new entry written in, and the form initialed and dated by the individual making the correction. Original records, source data, printouts from medical devices will be documented in a separate patient file.

Any copies of source data printouts related directly to the study that will be collected by the monitor will have only the subject number entered as an identifier (any personal subject information will be made illegible (e.g., blacked out) by the site staff in order to maintain the subject´s confidentiality).

11.1 Study records requirements

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]), be retained by the investigator for as long as needed to comply with national and international regulations (generally 25 years after discontinuing clinical development or after the last marketing approval). According to local regulations it is the Sponsor's responsibility to store essential documents. The investigator agrees to adhere to the document/records retention procedures by signing the protocol.

11.2 Data management

Data Management procedures will follow applicable regulations, all details will be separately described in a study-specific Data Management Plan (DMP) prepared by the responsible data manager (DM) and finalized and signed by both DM and designee of the Sponsor to the start of data entry for the first enrolled patient.

Verified and validated electronic data capture (EDC) will be utilized for capturing data. The eCRF application will be accessible by connecting to a dedicated server via a secure website. Each member of the study team has a password protected login with an individual username identifying the single user. Depending on the assigned tasks in the clinical investigation, only the access rights necessary to complete the assigned tasks are given by allocating each user to one out of a set of pre-defined user roles. The EDC system and processes will be described in more detail in the DMP.

Data entry into the eCRF is done in a pseudonymized manner. Each subject will be identified by a subject code not revealing the actual patient. Data entry into the eCRF is change-controlled via an extensive electronic audit trail within the EDC system. Automated checks for

completeness and consistency are performed directly on-line during data entry. In addition, manual quality control will be performed by the data manager. Both these check steps lead to system queries, that need to be answered within the EDC system used by the investigator or designee. Details of the processes will be described in the DMP, whereas the programmed validation checks are specifically listed in a study-specific Data Validation Plan (DVP). All data entered into the EDC system will be reviewed for completeness and evident recording errors will be rectified by contact with the appropriate clinical site. Computerized data checks will be used to identify unusual data entries for verification prior to statistical analysis. Queries resulting from automatic or manual consistency checks need to be answered by the investigator or designee directly within the EDC system.

To minimize the amount of missing data, investigators will be trained on the deleterious effect that missing data have on clinical investigation integrity and credibility and that missing data could diminish the scientific value of all subjects' altruistic contributions. In addition, all data important for study endpoint evaluations will be marked as required within the EDC system, so the investigator or designee will need to explain missing values electronically.

After completion and cleaning of data, the database is locked, and the data exported for statistical analysis.

Entries made in the eCRF and the corresponding entire query communication must be in English language for all participating countries and its trial sites and the monitors.

11.3 Archiving

All CRFs, informed consent forms and other important study materials will be archived for at least 25 years, after the study was deregistered by the competent authorities and ethic committees.

Essential documents shall be archived in such a way that ensures that they are readily available upon authorities’ request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the institution. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The Investigator/institution notifies the sponsor if the archival arrangements change (e.g., relocation or transfer of ownership). The ISF and the PSF is not to be destroyed without the sponsor’s approval. The Investigator’s contract will contain all regulations relevant for the trial site.

11.4 Monitoring

The study site will be monitored to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the study subject’s safety and rights as a study participant are respected, that accurate, valid, and complete data are collected, and that the study is conducted in accordance with the study protocol, the principles of GCP and local legislation.

All investigators agree that the monitor will regularly visit each study site and assure that the monitor will receive appropriate support in his/her activities at the study site, as agreed in separate contracts with each site. The declaration of informed consent includes a statement

to the effect that the monitor has the right – while observing the provisions of data protection legislation – to compare the CRFs with the study subject's medical records (physician´s notes, laboratory printouts etc.). A Source Document Checklist will be used at site to identify the source data for all points collected. The Investigator will ensure access for the monitor to all necessary documentation for study-related monitoring. The purposes of the monitor visits are as follows:

- Check the informed consent
- Check inclusion and exclusion criteria
- Monitor study subject safety (occurrence and documentation/reporting of AEs and SAEs)
- Check the completeness and accuracy of entries on the CRFs
- Validate the entries on the CRFs against those in the source documents (source data verification)
- Perform drug accountability checks
- Evaluate the progress of the study
- Evaluate compliance with the study protocol
- Assess whether the study is being performed according to GCP at the study site
- Discuss with the Investigator aspects of study conduct and any deficiencies found

A monitoring visit report will be prepared for each visit describing the progress of the clinical study and any problems (e.g., refusal to give access to documentation).

Further details will be given in the Monitoring Manual, including details on the use of remote and centralized monitoring techniques within a risk-based monitoring framework.

11.5 Audits/inspections

As part of quality assurance, the sponsor has the right to audit the study site and any other institutions involved in the study. The aim of an audit is to verify the validity, accuracy and completeness of data, to establish the credibility of the clinical study, and to check whether the study subject's rights and study subject safety are being maintained. The sponsor may assign these activities to persons otherwise not involved in the study (auditors). These persons are allowed access to all study documentation (especially the study protocol, case report forms, study subjects' medical records, drug accountability documentation, and study-related correspondence).

In addition, inspections by regulatory health authority representatives and EC/IRB are possible. The Investigator should notify the sponsor immediately of any such inspection.

The Investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

All persons conducting audits will keep all study subject data and other study data confidential.

12 Ethical and regulatory aspects

12.1 Independent ethics committee

The protocol, ICF and any other supporting study documents will be reviewed by an independent ethics committee (IEC). Each study site may not begin the study until the responsible ethics committee for that site has given its written approval, signed by the authority chairperson or authorized personnel, and a copy of the approval letter and the approved ICF for that site have been provided to the Investigator.

12.2 Notification of the authorities, approval and registration

Before the start of the clinical study, all necessary documentation will be submitted to the competent supreme federal authority for approval. The state authorities in each federal state in which the study will be conducted will also be notified.

Prior to start of the study, it will be registered under *www.clinicaltrials.gov*.

12.3 Ethical basis for the clinical study

This protocol is designed to ensure that the sponsor and investigator(s) abide by Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki and local regulations governing the conduct of clinical studies.

Documented approval from appropriate IECs will be obtained for all participating centers before start of the study. When necessary, an extension, amendment or renewal of the EC approval must be obtained. Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct, i.e., the investigator is not allowed to modify the procedures described in this protocol.

Modifications to the study protocol should be implemented only after agreement between sponsor, CPI and investigator(s). However, the investigator or the sponsor may implement a change of the protocol to eliminate an immediate hazard to the study subjects without prior IEC/sponsor approval/favorable opinion. As soon as possible, the implemented change and the reasons for it should be submitted to the IEC/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

All investigators and other staff involved in the study will be informed that the competent federal authorities and authorized representatives of the sponsor have the right to review study documentation and the study subjects' medical records at any time.

Details on discontinuation of the entire study or parts thereof can be found in section 5.3.

12.4 Obtaining informed consent from study subjects

All relevant information on the study will be summarized in a subject information sheet and informed consent form (ICF) provided by the sponsor. A sample subject information and ICF is provided as a document separate to this protocol.

Based on the subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject prior to her/his entry into the study (i.e., before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms). The investigator will also mention that

written approval of the IEC has been obtained.

Each subject will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject voluntarily agrees to sign the informed consent form and has done so, may she/he enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The ICF will be signed in duplicate, one copy remains with the subject and the second original is to remain in the ISF or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that informed consent was obtained prior to these procedures.

The ICF and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written ICF. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm her/his participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IECs approval / favorable opinion in advance of use.

Part of the monitoring activities are to check that the most recent ICF was used before the study subject was enrolled and that it was dated and signed by the study subject himself or herself.

12.5 Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject, for whom the deviation from protocol was detected, is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation.

12.6 Compensation for health damage of subjects

Patients will be insured by the sponsor against injury caused by their participation in the study according to legal requirements. The patients will be informed about the insurance and the requirements on their part.

12.7 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and / or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the sponsor. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest

confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential. The investigator will maintain a list to enable subjects to be identified in the ISF.

13 Publication

It is planned to publish the study results, in mutual agreement with the National Coordinating Investigators and the Sponsor´s Medical Expert, in a scientific journal and at German or international congresses. Publication of the results of the study as a whole is intended. Any publication will take account of the 'Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors (ICMJE)).

The study will also be registered in a public register (www.clinicaltrials.gov) in accordance with the recommendations of the ICMJE.

Any published data will observe data protection legislation covering the study subject and investigators. Success rates or individual findings at individual study sites are known only to the sponsor.

Publications or lectures on the findings of the present clinical study either as a whole or at individual investigation sites must be approved by the sponsor in advance, and the sponsor reserves the right to review and comment on such documentation before publication.

By signing the contract to participate in this study, the investigator declares that he or she agrees to submission of the results of this study to national and international authorities for approval and surveillance purposes, and to the Federal Physicians Association, the Association of Statutory Health Fund Physicians and to statutory health fund organizations, if required. At the same time, the investigator agrees that his or her name, address, qualifications and details of his or her involvement in the clinical study may be made known to these bodies.

14 Amendments to the study protocol

To ensure that comparable conditions are achieved as far as possible at individual study sites and in the interests of a consistent and valid data analysis, changes to the provisions of this study protocol are not planned. In exceptional cases, however, changes may be made to the study protocol. Such changes can only be made if agreed by the sponsor, sponsor's representative, the CPI and statistician, and all authors of this study protocol. Any changes to the study procedures must be made in writing and must be documented with reasons and signed by all authors of the original study protocol.

Amendments made in accordance with § 10 Secs. 1 and 4 GCP Regulations that require approval are submitted to the ethics committee and the supreme federal authority and will not be implemented until approved. Exceptions to this are amendments made to avoid immediate dangers.

15 References

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16 Appendices

16.1 Appendix I: Myelodysplastic Syndromes World Health Organization Classification System (2016)

According to: Arber DA, Orazi A, Hasserjian R, Thiele J, Borwitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391-405.

Subtype	Dysplastic lineages	Cyto-penias[1]	Ring sideroblasts in erythroid elements of BM	Blasts	Cytogenetics
MDS-SLD	1	1 or 2	RS<15% (or <5%[2])	PB <1% BM <5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)
MDS-MLD	2 or 3	1-3	<15% (or<5%[2])	PB <1% BM <5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)
MDS-RS					
MDS-RS-SLD	1	1 or 2	≥15% (or ≥5 %[2])	PB <1% BM <5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)
MDS-RS-MLD	2 or 3	1-3	≥15% (or ≥5 %[2])	PB <1% BM <5% No Auer rods	Any, unless fulfills criteria for isolated del(5q)
MDS with del(5q)	1-3	1-2	None or any	PB <1% BM <5% No Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS-EB					
MDS-EB1	0-3	1-3	None or any	PB 2~4% or BM 5~9%, no Auer rods	Any
MDS-EB2	0-3	1-3	None or any	PB 5~19% or BM 10%~19% or Auer	Any
MDS-U (unclassifiable)					
with 1% blood blasts	1-3	1-3	None or any	PB=1%[3] BM<5% Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	PB <1% BM <5% No Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15%[4]	PB <1% BM <5% No Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	PB <2% BM <5% No Auer rods	Any

[1] cytopenias defined as hemoglobin <100 g/L, Platelets <100 x 10^9/L, ANC <1.8 x 10^9/L
[2] with SF3B1 mutation
[3] 1% PB blasts must be recorded on at least two separate observations
[4] If with ≥15% ring sideroblasts and significant erythroid dysplasia, and are classified as MDS-RS-SLD.

16.2 Appendix II: International Prognostic Scoring System Score Revised (IPSS-R)

According to: Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120(12):2454–65.

Points for calculation							
	0	**0.5**	**1**	**1.5**	**2**	**3**	**4**
% blasts in BM	≤ 2	-	> 2 - < 5	-	5 - 10	> 10	-
Karyotype	very good[1]	-	good[2]	-	inter-mediate[3]	poor[4]	very poor[5]
Hemoglobin (g/dl)	≥ 10	-	8 - < 10	< 8	-	-	-
Platelets (/nl)	≥ 100	50 - < 100	< 50	-	-	-	-
Neutrophils (/nl)	≥ 0.8	< 0.8	-	-	-	-	-

Risk Score	
Very low risk	≤ 1.5
Low risk	> 1.5 - 3
Intermediate risk	> 3 – 4.5
High risk	> 4.5 - 6
Very high risk	> 6

For IPSS-R classification you can also use the “MDS Center” App which is available in the Apple Store or Google Play Store.

16.3 Appendix III:

a) Combined response assessment criteria for MDS and AML

Based on IWG 2018 criteria (MDS)[1] and the criteria of the European LeukemiaNet (AML)[2]

CATEGORY	DEFINITION
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 x 10^9/L (1000/µL); platelet count ≥100 x 10^9/L (100 000/µL)
CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia (<1.0 x 10^9/L [1000/µL]) or thrombocytopenia (<100 x 10^9/L [100 000/µL])
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to ≥5%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Stable disease (SD)	Absence of CR, CR_i, PR, MLFS; and criteria for PD not met
Progressive disease (PD)	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15%-point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (>0.5 3 10^9/L [500/µL], and/or platelet count to >50 x 10^9/L [50 000/µL] non-transfused); or • >50% increase in peripheral blasts (WBC x % blasts) to >25 x 10^9/L (>25 000/µL) (in the absence of differentiation syndrome)†; or • New extramedullary disease
Hematologic relapse (after CR, CR_i)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease
Hematologic improvement (HI)	
Erythroid response (**HI-E**)	
NTD (0 RBCs in 16 wk)*	At least 2 consecutive Hb measurements ≥1.5 g/dL for a period of minimum 8 wk in an observation period of 16 to 24 wk compared with the lowest mean of 2 Hb measurements (apart from any transfusion) within 16 wk before treatment onset‡; only a response duration of at least 16 wk, however, is considered clinically meaningful
LTB (3-7 RBCs in 16 wk in at least 2 transfusion episodes, maximum 3 in 8 wk)*	Transfusion independence, defined by the absence of any transfusions for at least 8 wk in an observation period of 16-24 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment; only a response duration of at least 16 wk, however, is considered clinically meaningful
HTB (≥8 RBCs in 16 wk, ≥4 in 8 wk)	Major response: Major HI-E response in HTB patients corresponds to transfusion independence, defined by the absence of any transfusions over a period of minimum 8 wk in an observation period of 16-24 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment; only a response duration of at least 16 wk, however, is considered clinically meaningful Minor response: Minor HI-E response in HTB patients is defined as a reduction by at least 50% of RBCs over a minimum of 16 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment

Platelet response (**HI-P**) (pretreatment, < 100 x 10^9/L)	• Absolute increase of 30 x 109/L for patients starting with >20 x 109/L PLTs or • Increase from <20 x 10^9/L to >20 3 10^9/L and by at least 100% In addition, • Evolution of bleeding symptoms is to be taken into account • Increments of platelets also for patients with a pretreatment PLT count of >100 x 10^9/L are to be reported
Neutrophil response (**HI-N**) (pretreatment, all patients)	• At least 100% increase and an absolute increase >0.5 x 109/L • (pretreatment, <1.0 x 10^9/L) • Increments of neutrophils also for patients with a pretreatment ANC of >1.0 x 10^9/L are to be reported
Progression or relapse after HI‡	At least 1 of the following: • At least 50% decrement from maximum response levels in granulocytes or platelets • Reduction in Hb by ≥ 1.5 g/dL • Transfusion dependence

†Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

b) IWG 2023 response criteria for HR-MDS

For secondary endpoint and MDS population only

RESPONSE	DEFINITION
Complete remission (CR)	• BM: <5% myeloblasts;* dysplasia may persist • PB: Hb ≥10 g/dL, platelets ≥100 × 109/L; neutrophils ≥1.0 × 109/L; blasts 0%†
CR equivalent*	Patients with <5% BM blasts at baseline: • BM: <5% myeloblasts*; dysplasia may persist • PB: Hb ⩾10 g/dL, platelets ⩾100 × 10^9/L; neutrophils ⩾1.0 × 10^9/L; blasts 0%† • Full cytogenetic clearance of baseline abnormalities (complete cytogenetic response)
Partial remission (PR)	All CR criteria except: • BM blasts decreased by ≥50% over pretreatment but still ≥5% • Cellularity and morphology not relevant
CR_L§ (CR_{uni} and CR_{bi})	• BM: <5% myeloblasts*; dysplasia may persist • PB: blasts 0%† • CR_{uni}: PB, not meeting CR but only 1 of the following: Hb ≥10 g/dL; platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L • CR_{bi}: PB, not meeting CR but only 2 of the following: Hb ≥10 g/dL; platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L
CR_h§	• BM: <5% myeloblasts*; dysplasia may persist • PB: Not meeting criteria for CR or CR_L, no Hb threshold required, platelets ≥50 × 10^9/L; neutrophils ≥0.5 × 10^9/L; blasts 0%†
HI	HI defined according to IWG 2018 response criteria:‖ • Not meeting criteria for CR (or CR equivalent) or CRuni or CRL • $HI_{erythroid}$ (HI-E) • $HI_{platelets}$ (HI-P) • $HI_{neutrophils}$ (HI-N)
ORR	ORR = CR (or CR equivalent)* + PR + CR_L + CR_h + HI
No response	Not meeting criteria for CR (or CR equivalent)*, PR, CR_L, CR_h, or HI‡
Not evaluable	All registered/randomly assigned patients should be reported in the denominator of response assessment analyses in line with the intention-to-treat principle. This category may include patients yet to have a response assessment, suffering early

	death, exiting the study early, or those with a technically suboptimal BM sample precluding assessment.
Cytogenetic response¶	• Complete: disappearance of the chromosomal abnormality without appearance of new ones. • Partial: ≥50% reduction of the chromosomal abnormality.
Progressive disease (PD)	Fulfilling any of the criteria below: #,∗∗,†† • Disease progression by blasts: ≥50% relative increase in blasts and absolute increase of blast percentage by at least 5% from pretreatment sample taken before current line of therapy • Disease progression by worsening cytopenia: new, repeated (more than once and separated by ≥7 days) need for RBC or platelet transfusions within 8 weeks, not related to acute intercurrent illness (eg, sepsis, gastrointestinal tract bleed) or treatment effect, in the absence of HI of at least one other blood lineage as defined above • Progression to AML: ≥50% increase in blasts from baseline assessment to ≥20% blasts.
Disease relapse	Fulfilling any of the criteria below[#]: • Disease relapse by blasts: absolute and relative increase in BM blasts by at least 5% and ≥50%, respectively, from prior assessment, or reappearance of blasts in the blood, or development of extramedullary disease (myeloid sarcoma). • Disease relapse by worsening cytopenias: decrement in one or more blood cell lineage counts by ≥50% from maximum remission/response levels for platelets or absolute neutrophil count or a reduction of Hb by 1.5 g/dL combined with an absolute reduction in the same lineage(s) as follows: Hb <10 g/dL, platelets <100 × 10^9/L, or absolute neutrophils <1.0 × 10^9/L or repeated (more than once and separated by ≥7 days) need for RBC or platelet transfusions which are not related to acute intercurrent illness (eg, sepsis, gastrointestinal tract bleed) or treatment effect; in the absence of HI of at least one other blood lineage as defined above.
Patient reported outcomes (PROs)	Reporting by means of a validated assessment tool is encouraged[‡‡]

∗ Patients require ≥5% blasts before treatment initiation to be considered evaluable for CR, PR, CRh, or CRL. For time window of response assessment by PB counts, refer to Table 5 in the publication on the criteria (Zeidan et al., 2023). For patients with <5% blasts who have HR-MDS owing to adverse cytogenetics and/or severe cytopenias, full cytogenetic clearance (complete cytogenetic response) and blood counts that meet CR criteria are considered CR equivalent but should be reported separately. Full trilineage count recovery is defined as Hb ≥10 g/dL, platelets ≥100 × 10^9/L, and ANC ≥1.0 × 10^9/L independent of baseline PB. Given that molecular clearance has not been validated prospectively, it was not used for CR definition.

† For discrepancy between BM and PB blast percentage, refer to Table 5 in the publication on the criteria (Zeidan et al., 2023).

‡ A few panelists felt that mCR could still have a value, especially in bridging patients to allo-HSCT, and should therefore, still be reported. If mCR is reported, it should not be included in the ORR. Prolonged SD (≥16 weeks) might have limited benefit in patients with HR-MDS who are not candidates for allo-HSCT. However, SD is a function of time of stability, and in single-arm studies without a control arm, it is challenging to assess whether SD reflects more indolent MDS biology in some patients vs the impact of therapy. Furthermore, disease stability is included as part of the PFS definition. Therefore, SD should not be included in the ORR.

§ CR_L and CR_h are provisional entities that require additional prospective validation. Both CR_L and CR_h are included to allow prospective validation of their value in MDS. Similar to CR and PR, both are defined by blood counts at or around the time of response assessment and independently of the baseline blood counts. To be eligible for CR_L, patients need to have achieved PB count levels at or around the time of assessment in 1 or 2 lineages, but not in all 3 lineages, that are at or above the CR threshold for the specific lineage(s). In patients with MDS/AML or MDS with increased blasts as defined by the 2022 International Consensus Classification and the 5th edition of WHO classification, respectively, reporting CR_h defined as <5% blasts in the BM, 0% PB blasts, and partial recovery of PB counts (platelets ≥50 × 10^9/L and ANC ≥0.5 × 10^9/L) can be considered to achieve consistency with ELN 2022 AML response criteria. Similar to CR_L, CR_h is considered a provisional response category in MDS and requires additional prospective validation. If patients meet criteria for both CR_L and CR_h, they should be reported as having achieved CR_L for the ORR as it represents a higher threshold for hematologic improvement.

‖ For screening period and time window for assessment of transfusion dependency/independence, refer to Table 5 in the publication on the criteria (Zeidan et al., 2023)

¶ If cytogenetic analyses fail, repeating cytogenetics during a subsequent response assessment is recommended. MRD assessment in MDS is insufficiently validated at this time as a surrogate for OS. MRD-negative response can be reported as a provisional response category, and clinical trial protocols should predefine what techniques are used to detect MRD and what cutoffs are considered to define an MRD response.

BM biopsy to assess for disease progression is recommended. In patients with disease progression/relapse defined by the need for transfusion support, the date of the first unit of RBC and platelet transfusion will be the date of disease progression.

∗∗ Clonal progression (defined as the acquisition of new cytogenetic or molecular abnormalities) can be reported as a provisional progression criterion. This does not necessarily constitute clinical progression unless otherwise specified by the protocol.

†† For patients with <5% BM blasts from pretreatment sample before current line of therapy, the definition of PD might be applied to patients with ≥50% relative BM blast count increase who do not have an absolute increase of ≥5% blasts in the right clinical context (eg, worsening disease-related cytopenias). Similarly, for patients with an absolute BM blast increase to ≥20% but who have <50% relative BM blast count increase from pretreatment before current line of therapy, this could denote progression in the right clinical context where additional therapeutic options may be available with a new diagnosis of AML.

‡‡ The panel recognizes that improvements in PROs (including health-related quality of life or symptoms) can be a meaningful, patient-centered goal of treatment. However, there is not yet sufficient evidence in HR-MDS to support specific recommendations at this point. In any case, rigorous assessment of PROs in clinical trials is recommended.

16.4 Appendix IV: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-55.

16.5 Appendix V: Sample of QoL questionnaire

A PDF file of the EORTC QLQ-C30 can be downloaded without charge at:

https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf

(Access date: March 18th, 2022)

16.6 Appendix VI: CTCAE Version 5.0

Toxicity will be scored using CTCAE Version 5.0 for toxicity and adverse event reporting.

A PDF file of CTCAE v 5.0 can be downloaded without charge at

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Published: November 27th, 2017

16.7 Appendix VII: List of prohibited concomitant medications

The following medications are prohibited during the study:

- ESAs therapy
- Chemotherapy
- Hypomethylating agents
- Immunotherapy
- Any experimental therapy / study drug other than imetelstat
- Corticosteroids
    - Systemic use of corticosteroids in excess of prednisone 20 mg/day or its equivalent for more than 10 days is prohibited unless reviewed and approved by the sponsor's medical monitor.
    - Long-term, chronic use of corticosteroids at any dose should also be reviewed and approved by the sponsor's medical monitor.
    - Corticosteroids used as premedication are permitted.

The following medications can be applied after prior discussion with the sponsor:

- Radiotherapy
- Immunomodulatory agents (eg, lenalidomide),

The following concomitant anti-leukemic medication is allowed:

- Hydroxyurea is allowed
- Radiotherapy is allowed at the discretion of the sponsor
- All other anti-leukemic treatments are prohibited

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