STATISTICAL ANALYSIS PLAN

IMpress Study

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

Sponsor: GCP-Service International West GmbH
Siegfeldstraße 11
53721 Siegburg, Germany
Phone: +49 (0) 421 89 67 66 11
Fax: +49 (0) 421 89 67 66 48
E-mail: germany@gcp-service.com

Author: [redacted]
GCP-Service International Ltd. & Co. KG
Anne-Conway-Str. 2
28359 Bremen, Germany
Tel [redacted]

Date of document: 13.10.2025

Document version: 3.0

NCT05583552

Document History

Version	Date	Author(s)	Description
v0.1	21-SEP-2023	[redacted]	First draft
v1.0	23-FEB-2024	[redacted]	Finalization
v1.1	03-SEP-2024	[redacted]	Substantial modification after interim analysis based on interim analysis data showing no responders according to response assessment criteria.
V2.0	19-DEC-2024	[redacted]	Finalization
V2.1	09-OCT-2025	[redacted]	• Trial schedule update after Protocol amendment v6.0 (see 2.4) • Rename of section 7.7.3 and addition of censoring in section 7.7.13 • Update of references errors • Inclusion of baseline characteristics tables and listings (see 8.2.2) • Inclusion of Serum chemistry and Vital Signs tables (see 8.5.4) for the analysis aligning with protocol section 10.9.4

			• Inclusion of Dose Modifications listing (see 8.5.3) aligning with protocol section 10.9.2) • Restructuring of sections 6.1, 6.2.3, 8.5.3, 8.5.4, 8.6 and 8.7 for a better structure of the additional endpoints. Extent of exposure and laboratory other endpoints moved to safety endpoint to be analysed in SES aligning with protocol sections 10.9.2 and 10.9.4.
V3.0	13-OCT-2025	[redacted]	• Finalization

Signatures

I confirm that this Statistical Analysis Plan accurately describes the planned statistical analyses to the best of my knowledge and was finalized before data review meeting.

Author: [redacted]
Biostatistician
GCP-Service Int. Ltd. & Co. KG
Anne-Conway-Straße 2
28359 Bremen, Germany

Date Signature

Reviewer: [redacted]
Biostatistician
GCP-Service Int. Ltd. & Co. KG
Anne-Conway-Straße 2
28359 Bremen, Germany

Date Signature

Approved: [redacted]
Chief Executive Officer
GCP-Service International West GmbH
Regional Office
Siegfeldstr. 11
53721 Siegburg, Germany

Date Signature

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List of Abbreviations and Key Terms

Abbreviation	Definition
α	Type I error
ß	Type II error
AE	Adverse Event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute Neutrophil Count
ATC	Anatomical Therapeutic Chemical
AUS	Australia
BID	Twice per day
BM	Bone marrow
BMI	Body Mass Index
BSC	Best supportive care
CBC	Complete blood count
CFB	Change from baseline
CI	Confidence Interval
CPI	Coordinating Principal Investigator (*Leiter der klinischen Prüfung*)
CR	Complete Remission
CRi	Complete Remission with Incomplete recovery
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DRM	Data Review Meeting
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status

eCRF	Electronic case report form
EOS	End of Study
EOT	End of Treatment
FAS	Full analysis set
FU	Follow-up
GCP	Good clinical practice
Hb	Hemoglobin
HI	Hematologic Improvement
HI-E	Hematological improvement - erythroid
HI-N	Hematological improvement - neutrophils
HI-P	Hematological improvement - platelets
HMA	Hypomethylating agents
HRQoL	Health-Related Quality of Life
IA	Interim Analysis
ICF	Informed consent form
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
IWG	International Working Group
LDH	Lactate Dehydrogenase
LPEOS	Last patient end of study
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic Leukemia-Free State
Min	Minimum

Max	Maximum
Miss	Missing observations
NCI	National Cancer Institute
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
PRN	As needed
PT	Preferred Term
Q2W	Every two weeks
Q1	Lower quartile
Q3	Upper quartile
QD	Per day
QID	4 times per day
QIMRB	Queensland Institute of Medical Research Berghofer
QOD	Every other day
QoL	Quality of life
QM	Per month
RBC	Red blood cell
RDW	Red blood cell distribution width
RS	Raw Score

S	Final Score
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDTM	Study Data Tabulation Model
SDev	Standard Deviation
SES	Safety Evaluation Set
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TEAEs	Treatment emergent adverse events
TID	3 times per day
ULN	Upper limit of normal
UMVUE	Uniformly minimum variance unbiased estimator
WBC	White blood cell count
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) contains a more technical and detailed elaboration of the principal features of the statistical analyses as described in the Study Protocol IMpress_001, version v6.0, dated 03-SEP-2025. The purpose of the SAP is to serve as a guideline for statistical programming and creation of analysis tables, figures, and listings for the clinical study report. Therefore, this document has to be finalized and signed before the data review meeting and start of the statistical analysis.

2. Study Description

2.1 Study Design

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.

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 (Section 11.2 Appendix 2). 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 7.7.4) 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 section 11.2 Appendix 2 a)), withdraws consent, or meets any other discontinuation criteria defined in section 2.1.8.

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 study protocol v6.0 (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 2.1.8 are met.

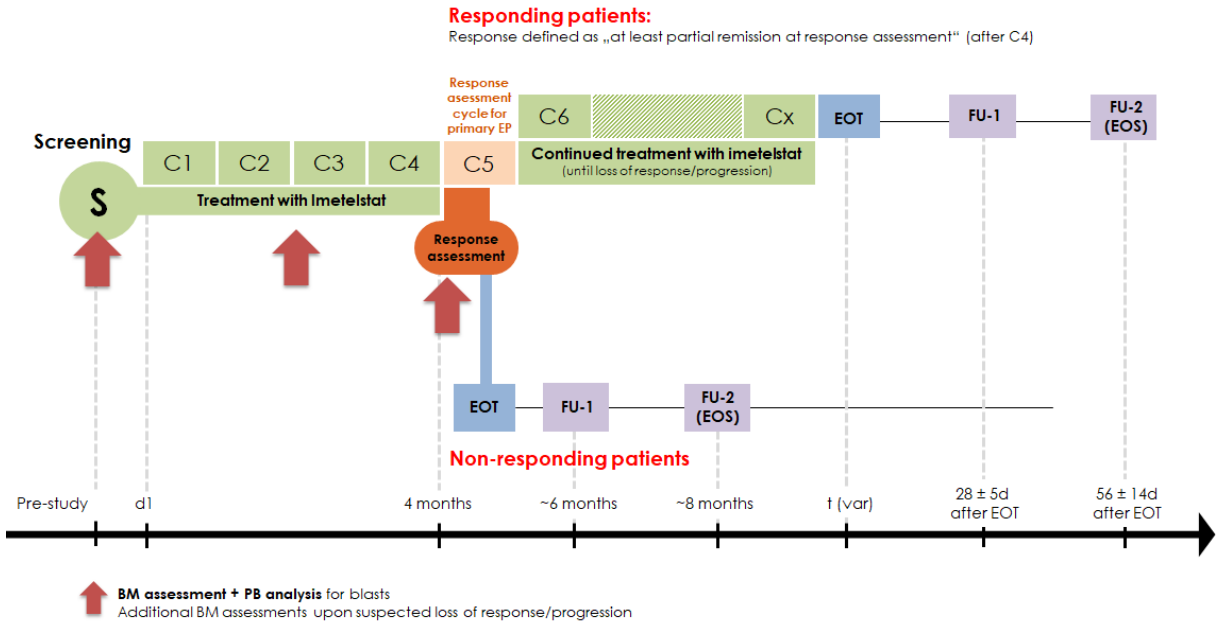
Patients who stop the study treatment for any cause will undergo an EOT visit at the latest 14 days after the decision of treatment discontinuation. The EOT visit will be followed by a first follow-up visit (FU1) 28 ± 5 days after EOT and a second FU visit = EOS visit approximately 2 months after EOT. 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 2.4.

Figure 1: Study flowchart



2.1.1 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).

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

Imetelstat sodium will be administered at a dose of 7.5 mg/kg, i.v., Q2W. Subjects will receive imetelstat on day [redacted] and day [redacted] of each [redacted] day treatment cycle (see 2.4 (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] cycles 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 2.1.8.

2.1.3 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 cycle [redacted] (performed at the beginning of cycle [redacted] is the primary endpoint (pEP) assessment.

Based on the outcome of the disease assessment in cycle [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 (cycle [redacted] / week [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 2.1.4). 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 of the protocol are met. These subjects will follow the assessments and procedures according to the schedule of assessments for the extension phase (section 2.4, Part 2c). Responders who have BM blasts ≥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)[4] and the criteria of the European LeukemiaNet (AML)[5] in order to harmonize the criteria for MDS and AML patients in this trial. The combined criteria are listed in section 11.2 Appendix 2 a).

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 2.4, Part 2c).

Patients with at least PR at this pEP assessment will continue in the extension phase described below in section 2.1.4.

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]). 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.

2.1.4 Extension phase of the treatment period ([redacted])

Subjects who meet the criteria to remain on treatment after completion of the cycle [redacted] / week [redacted] disease assessment and have BM blasts ≥ 5% may continue dosing on day [redacted] and day [redacted] of each [redacted]day 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] day 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 section 11.2 Appendix 2 a)), withdraws consent, or meets any other discontinuation criteria defined in section 2.1.8.

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 subjects 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 2.4 [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 2.1.3. 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 2.4, Part 2c).

2.1.5 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 2.4 (part 3).

2.1.6 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).

2.1.7 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 IA 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.

2.1.8 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)[4] and the criteria of the European LeukemiaNet (AML)[5]
- 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 2.4 Trial Schedule and section 2.1.5 Posttreatment follow-up (FU) period).

2.2 Treatments

Test drug:	Imetelstat sodium
Starting dose:	[redacted] mg/kg
Dosing regimen:	Every [redacted] weeks for [redacted] cycles of [redacted] days 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 either enter into an extension treatment period under investigator's discretion in case of a stable or controlled disease or discontinue Imetelstat treatment, undergo EOT and enter the follow-up phase of the trial.

Administration route: Intravenous (IV)

Imetelstat sodium dose modifications will be performed as described as follows: All dose modifications must be recorded in the eCRF.

Table 1: Dose titration

Titration		Dose regimen
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

2.2.1 Dose Modifications for Hematologic Toxicities

For any occurrence of [redacted]

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

2.2.2 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]

2.2.3 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.

2.2.4 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.

2.3 Objectives

2.3.1 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 first line hypomethylating agent (HMA)-based treatment.

2.3.2 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-C3)

2.4 Trial Schedule

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

VISIT NO.	[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]
Study Week		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle		[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
ECOG performance status	x									x	
BMI	x					x				x	
ECG	x										
Pregnancy test[4]	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.

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	
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	

[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.

[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 week [redacted] after ending cycle [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 cycle [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.

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	

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)									

[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)

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[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 cycle [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

2.5 Study Hypotheses

The study is designed as single-arm phase II trial. The design of the trial was focused on demonstrating that the trial efficacy (p) was greater than an undesired level of efficacy (p_0) which would indicate that the treatment is ineffective. The following statistical hypothesis would be tested in confirmatory way:

$$H_0: p \leq p_0 \quad \text{(Null hypothesis with } p_0 = 0.05\text{)}$$

vs.

$$H_1: p > p_0 \quad \text{(Alternative hypothesis)}$$

[redacted] Due to the transient improvement seen in WBC and peripheral blasts in patients early in treatment, the study will continue in an exploratory approach.

2.6 Sample Size Calculation

A Simon's two-stage design will be 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 α = 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 IA to ensure [redacted] evaluable patients for the IA.

[redacted]

Due to the transient improvement seen in WBC and peripheral blasts in patients early in treatment, the study will continue in an exploratory approach with a change in dose frequency.

2.7 Randomization and Stratification

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

[redacted]

Due to the transient improvement seen in WBC and peripheral blasts in patients early in treatment, the study will continue in an exploratory approach with a change in dose frequency. Therefore, two cohorts will be defined by treatment regimen:

- Cohort 1: Subjects screened before IA receiving dosage once in a [redacted]day cycle for at least [redacted] cycles
- Cohort 2: Subjects screened after IA receiving dosage twice in a [redacted]day cycle (once every [redacted] days) for at least [redacted] cycles

2.8 Blinding

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

2.9 Planned Interim or Sequential Analysis

Simon's two stage design is used in this study, with an IA at the first stage following assessment of [redacted] evaluable patients. If the number of responses is less than or equal to [redacted] out of [redacted] patients in the first stage, then the trial will be stopped for futility. The final analysis will be conducted based on the total evaluable [redacted] patients if there are [redacted] or more responses in the first stage.

Further details regarding the planned IA are provided in Section 5.

2.10 Handling of Changes to Study Protocol

In case of prospective changes to the planned analyses that represent a substantial deviation from the protocol, these will be added to and explained in the clinical study protocol in a substantial protocol amendment. Any prospective changes that do not fulfil the requirements for a major protocol amendment should be included in an update to the SAP that should be finalized prior to database lock. All deviations and/or alterations from the envisaged analysis that occurred after database lock and their reasons will be described and discussed in detail the clinical study report (CSR).

3. Technical Aspects

3.1 General Aspects

All programs will be written using SAS® Version 9.4 or higher. There will be an individual SAS® program written for each table, figure, and listing, where tables or figures generated for different subgroups do not necessarily require separate programs. Each analysis program will be validated by a second qualified SAS® programmer to ensure a correct output and a correct presentation of the data. The validation process is documented in the validation sheet (GCPS_DMF_033 A-C), which also prespecifies criteria for risk categorization of programs and the corresponding validation actions.

All outputs will be generated in English language as RTF documents with DIN A4 format and will be saved as write-protected PDF documents with tables of contents preceding the content of the file. There will be one RTF/PDF document for tables, one for figures and one for listings. Courier New is used as font. The font size should be consistent within each document and reasonable, i.e., there should be as much required information as possible on one page, but the text should still be easy to read.

In headings, titles, and listings only the first word will be capitalised. If missing data are displayed in a subject listing, they are represented as blank field. Listings will be sorted by subject number unless specified otherwise. A list of all planned tables, figures and listings can be found at the end of this SAP and the layout of these tables and listings is provided in the documents IMpress_YYYYMMDD_mockTables_v1.0 and IMpress_YYYYMMDD_mockListings_v1.0

3.2 Data Conversion

Final study data will be converted into the Study Data Tabulation Model (SDTM) defined by the Clinical Data Interchange Standards Consortium (CDISC). EDC data as well as external data (e.g., laboratory data and protocol deviations) will be mapped to SDTM according to SDTM Implementation Guide version 3.3 and NCI Controlled Terminology in effect at the time the conversion is started will be followed.

The final SDTM domains will be used to generate analysis datasets according to the Analysis Dataset Model (ADaM) defined by CDISC. The data from the SDTM domains will be mapped to ADaM datasets according to the ADaM Implementation Guide version 1.2 and NCI Controlled Terminology in effect at the time the conversion is started will be followed.

The ADaM datasets will support each statistical analysis described in this SAP. Deviations have to be agreed with the Sponsor and at least described in the Analysis Data Reviewer's Guide.

4. Analysis Sets and Subgroups

4.1 Analysis Sets

4.1.1 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.

4.1.2 Per Protocol Set (PPS)

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

4.1.3 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.

4.2 Subgroups

To explore separately the efficacy of imetelstat, the analysis of the primary endpoint will be repeated by WHO classification (MDS/AML).

5. Interim Analysis

There will be two analyses during this trial:

- An IA at the first stage following assessment of [redacted] evaluable patients.
- A final analysis based on the total evaluable [redacted] patients if there are [redacted] or more responses in the first stage.

The following data will be analysed at the IA:

- Listing of baseline blasts in bone marrow.
- Safety variables (Serious Adverse Events (SAEs), hospitalisations, death due to toxicity and death due to disease).

- Responder (see section 6.2.1, including type of responses, mean blasts in bone marrow (BM cytology assessment) and hematology (automated CBC) baseline value and AML or MDS WHO classification.

6. Analysis Variables and Study Endpoints

6.1 Disposition, Demographic and Baseline Variables

Disposition	• Screened (defined as signed ICF)
	• Screening Failure (defined as signed ICF, but terminate the study for any reason before first treatment with IMP)
	• Enrolled (defined as signed ICF and all inclusion/exclusion criteria fulfilled)
	• Treated (defined as receiving IMP at least once)
	• Enrolled in extension treatment phase (from cycle 5 until loss of response)
	• Completed the study
	• Discontinuation study
	  ○ Screening Failure
	  ○ Withdrawn by subject
	  ○ Adverse Event
	  ○ Lost of Follow Up
	  ○ Protocol deviation
	  ○ Pregnancy
	  ○ Death
	  ○ Physician decision
	  ○ Other
	• Allocation to analysis sets (FAS, PPS, SES)
	• WHO Classification (MDS, AML)

Demographics	• Age (in years) • Gender (Male/Female) • Race (Black, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, Not reported, Other)
Baseline	• Transfusion history by type of transfusion (RBC, platelets, see 7.7.2 for derivation): o Number of units within 16 weeks o Mean pretransfusion levels (RBC or platelets, in g/dl or mcL) o Rate of units within 16 weeks • Vital signs o Height (in cm) o Weight (in kg) o BMI (in kg/m2) • ECG o PR interval (in msec) o QRS interval (in msec) o QT interval (in msec) o QTcF interval (in msec) o Heart rate (in beats/min) • IPSS-R score o % blasts in BM (≤ 2, > 2 - < 5, 5 – 10, > 10) o Karyotype (very good, good, intermediate, poor, very poor) o Hemoglobin (≥ 10 g/dl (≥ 6.2 mmol/l), 8 - < 10 g/dl (5 - <6.2 mmol/l), < 8 g/dl (<5 mmol/l)) o Platelets (/nl) (≥ 100, 50 - < 100, < 50)

	○ Neutrophils (/nl) (≥ 0.8, < 0.8) ○ IPSS-R score (very low risk, low risk, intermediate risk, high risk, very high risk) • WHO Classification (MDS, AML) ○ WHO 2016 Classification for MDS ○ WHO 2016 Classification for AML
Medical history/ Concomitant medication	• Prior and concomitant medical history (SOC and PT, see section 7.5.2) • MDS/AML related Medical History (Initial WHO 2016 Classification) • Concomitant Procedures • Concomitant medications (for derivation see section 7.5.4) • Prior and concomitant MDS/AML medications

6.2 Endpoints and Related Variables

6.2.1 Primary Endpoint

Objective	Endpoint
To assess the efficacy of imetelstat for the treatment of AML and MDS patients failing or being refractory to first line hypomethylating agent (HMA)-based treatment	Overall hematological response rate as assessed in week [redacted] of treatment with imetelstat using the combined response assessment criteria for MDS and AML (see Appendix 11.2 for more details). The main analysis will be based on the eCRF item “Is the subject classified to be a Responder according to protocol?” (RS_DSRESP).

6.2.2 Secondary Endpoints

Objective	Endpoint

To assess the safety of imetelstat	Toxicity is measured by TEAEs (see section 7.7.12), which will be coded using the MedDRA coding system (see section 7.5.1). All SOCs are rated by NCI CTCAE v5.0. Early toxicity will be estimated by toxicity until visit 3 (W5 C2). Time to first related TEAE with toxicity of grade 3 or higher.
To assess efficacy of imetelstat	Overall survival is defined as the time from the beginning of imetelstat treatment until death or censored at the date of the last observation in the study.
	Progression-free-survival is 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 the last observation.
	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 section 11.2 Appendix 2 a)) until the first date at which recurrent or progressive disease is objectively documented.
	Best overall response is 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).
To assess efficacy of imetelstat in the MDS population.	For MDS population only: Response based on IWG 2023 criteria (for definition see section 11.2 Appendix 2 b))
To assess efficacy of imetelstat.	Quality of life is measured using the scores of EORTC QLQ-C30 (version 3) • Global health status / QoL

	• Functional scales • Symptom scales / items

6.2.3 Other Endpoints

Endpoint
Vital signs • Height (in cm) • Weight (in kg) • BMI (in kg/m^2) • Systolic blood pressure [SBP] (in mmHg) • Diastolic blood pressure [DBP] (in mmHg) • Pulse rate (in beats/min) • Respiratory rate (breaths/min) • Body temperature (in °C) Physical examination (Normal/ Abnormal, nCS/ Abnormal, CS) for each body system • General appearance • Head – Eyes – Ears – Neck – Throat • Skin • Musculoskeletal system • Lymph nodes • Nervous system • Chest • Abdomen • Spine and limbs Laboratory parameters: • Serum chemistry

- Sodium (in mmol/L)
- Potassium (in mmol/L)
- Chloride (in mmol/L)
- Bicarbonate (if available) (in mmol/L)
- Calcium (in mmol/L)
- Magnesium (in mmol/L)
- Phosphate (in mmol/L)
- Urea nitrogen (in mmol/L)
- Creatinine (in mmol/L)
- Glomerular Filtration Rate, Estimated (in ml/min/1.73 m^2)
- Glucose (in mmol/L)
- Albumin (in mmol/L)
- Protein (in g/L)
- Alkaline phosphatase (in nkat/L)
- Bilirubin (in mmol/L)
- Aspartate Aminotransferase (in nkat/L)
- Alanine Aminotransferase (in nkat/L)
- Urate (in mmol/L)
- Gamma Glutamyl Transferase (in mmol/L)

- Automated complete blood count
  - Erythrocytes (T/L)
  - Leukocytes (in G/L)
  - Neutrophils (in 10^9/L)
  - Eosinophils (in G/L)
  - Basophils (in G/L)
  - Lymphocytes (in G/L)
  - Monocytes (in G/L)

- Haemoglobin (in g/dL)
- Haematocrit (in %)
- Nucleated Erythrocytes (in T/L)
- Reticulocytes (in T/L)
- Platelets (10^9/L)
- Ery. Mean Corpuscular Volume (in Fl)
- Ery. Mean Corpuscular Hemoglobin (in fmol)
- Ery. Mean Corpuscular HGB Concentration (in mmol/L)
- Erythrocytes Distribution Width (in %)

- Cytogenetic Analysis
  - Number of metaphases available for analysis (<20 or ≥ 20)
  - Karyotype (according to IPSS-R-Score: very good, good, intermediate, poor, very poor))
- BM Cytology Assessment
  - Blasts in Bone Marrow (in %)
  - Auer Rods (in %, not detectable is set to 0%)
  - Ringed Sideroblasts (in %, not detectable is set to 0%)
  - Dysplasia (>10% Dysplasia in Erythropoiesis (yes/no), >10% Dysplasia in Thrombopoiesis (yes/no), >10% Dysplasia in Granulopoiesis (yes/no))
- CBC with differential:
  - Neutrophils/Leukocytes (in %)
  - Promyelocytes/Leukocytes (in %)
  - Myelocytes/Leukocytes (in %)
  - Metamyelocytes/Leukocytes (in %)
  - Eosinophils/Leukocytes (in %)
  - Basophils/Leukocytes (in %)
  - Lymphocytes/Leukocytes (in %)

○ Monocytes/Leukocytes (in %) • PB blast assessment ○ Blasts (in %)
Transfusion history by type of transfusion (RBC, platelets, see 7.7.2 for derivation): • Number of units within [redacted] weeks before treatment and after first dose • Rate of units within [redacted] weeks before treatment and after first dose • Mean pretransfusion levels (g/dL for RBC, mcL for platelets) within [redacted] weeks before treatment and after first dose
Exposure to imetelstat: • Treatment compliance defined as number of doses until visit [redacted] divided by number of doses for [redacted] cycles. • Duration of treatment (in days) • Total dose (in mg), defined as the sum of all total calculated dose administrated until visit [redacted]. • Dose intensity as dose level administrated ([redacted])
Additional parameters: • ECOG Performance status (from 0= Fully active, able to carry on all pre-disease performance without restriction to 5 = Dead)

7. Data Handling

7.1 Handling of Missing Data and Outliers

If outliers, i.e., impossible, or very implausible values, occur, queries will be raised to the investigator who will either correct or confirm the value. If the value is confirmed, the analysis will be carried out with the outlier included. Complete exclusion of values should only be done in exceptional cases and is only valid for impossible and very implausible values with obvious justification. The decision to exclude data points from the statistical analysis is the joint responsibility of the sponsor, and the statistician. Outliers will be documented and, if applicable, their exclusion from analysis will be justified in the clinical study report.

Missing data will not be imputed.

7.2 Handling of Screening Failures, Withdrawals and Drop-outs

Data of withdrawals and drop-outs will be used as available.

Screening failures, i.e., subjects who have signed informed consent form but terminated the study for any reason before the first treatment will be replaced.

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.

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.

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

7.3 Data Review

Data are checked and cleaned during the course of the study. Protocol deviations such as time window deviations are identified during monitoring and by data management checks. The statistical programmer will collect the protocol deviations. Additional protocol deviations might be identified and added during this data review.

Classification of protocol deviations into critical and non-critical will be discussed between Sponsor and statistician prior to database lock, with the final decision being made by the Sponsor. A critical protocol deviation is defined as protocol deviation which might influence the outcome of the primary analysis (e.g., a violation of eligibility criteria detected after enrolment). The free choice of subjects to terminate their study participation prematurely is described in the study protocol and thus not regarded as protocol deviation but as reason for exclusion from the per protocol set. The following list of criteria can be used to identify critical protocol deviations and is not meant to be exhaustive:

- Violation against eligibility criteria
- Deviation from visit window of primary endpoint visits.
- Assessment of primary endpoint not performed
- Use of disallowed concomitant medication

For further details it is referred to the Data Review Meeting Plan (DRM).

7.4 Date Coding and Day Numbering

The format for presentation of date variables will be DDMMMYYYY (e.g., 21JAN2021). The format for presentation of time variables will be hh:mm (e.g., 09:02).

If dates are partially given, they will not be completed unless relevant to calculate durations. For such cases, a worst-case scenario will be assumed as follows:

- If the duration of an adverse event is calculated, the date is imputed to yield the highest possible duration.
- If the time to onset of an adverse event is calculated, the date is imputed to yield the shortest time to onset.

Deviations will be documented and explained. For date imputations related to medical history/concomitant diseases or prior/concomitant medication, refer to sections 7.5.2 and 7.5.4, respectively.

7.5 Coding Systems and Conventions

7.5.1 Coding of Adverse Events and Medical History

All medical terms reported as adverse events (AE) and as medical history/concomitant disease are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time the database is closed. At least the System Organ Class (SOC) as well as the Preferred Term (PT) should be available for the statistical analysis. Within each SOC and PT, AEs are graded using the CTCAE grades (Version 5.0) and accompanied by descriptions of severity (Grade).

7.5.2 Separation of Medical History from Concomitant Diseases

Separation of medical history from concomitant diseases will be done by comparison of the stop date of the medical condition with the date of the first treatment with study medication. Each finding will be allocated unambiguously either to medical history or concomitant disease.

- **Medical history:** If the stop date is before start of treatment or the stop date is partially given and unambiguously before start of treatment, the medical condition is allocated to medical history. Furthermore, if the stop date is missing and the medical condition is not known to be ongoing, findings coded as “Surgical and medical procedures” are also allocated to medical history.

- **Concomitant diseases:** If the stop date is at or after start of treatment or the medical condition is ongoing, the medical condition is referred to as concomitant disease. If the stop date is partially given and not unambiguously before start of treatment, the medical condition is allocated to concomitant diseases. If the stop date is missing and the medical condition is not known to be ongoing, the medical condition is allocated to concomitant diseases.

7.5.3 Coding of Medications

All medications are coded according to the Anatomical Therapeutic Chemical (ATC/DDD) classification system in effect at the time the database is closed. At least the ATC levels 2 and 3 should be available for the statistical analysis.

7.5.4 Separation of Previous and Concomitant Medications

Separation of previous from concomitant medications will be done by comparison of the stop date of the medication with the date of the first treatment with study medication. Each medication will be allocated unambiguously either to previous or concomitant medications:

- **Previous medication:** If the stop date is before start of treatment or the stop date is partially given and unambiguously before the start of treatment, the medication is allocated to previous medications.

- **Concomitant medication**: If the stop date is at or after the start of treatment or the medication is ongoing, the medication is referred to as concomitant medication. If the stop date is partially given and not unambiguously before start of treatment, the medication is allocated to concomitant medication. If the stop date is missing and the medication is not known to be ongoing, the worst case is assumed, and the medication is allocated to concomitant medication.

7.6 Rounding Rules

7.6.1 Estimates of the Mean and Standard Deviation

When using reported data, the mean and standard deviation will both be calculated to the least precise range.

When using data derived/calculated from reported data, the mean and standard deviation will both be calculated to at least two (2) extra digits more than the reported data and the result will be rounded to one more decimal place than the reported data. The rounding of the extra digits will be done according to the following rules (as conducted by default in SAS):

- If the second extra digit is less than five (5), it is dropped.
- If the second extra digit is greater or equal five (5), it is dropped, and the first extra digit is increased by one (1).

7.6.2 Other data

Quartiles, confidence intervals (CIs) and median will be presented with the same number of decimal places as the mean. Minimum and maximum will be presented with the same number of decimal places as the data used. For estimates of proportions, the result will be rounded to 3 decimal places. If proportions are displayed as percentage, 1 decimal place will be displayed. For example, a proportion of 0.655 will be presented in percentage as 65.5%.

7.7 Data Derivation

This section describes rules for the derivation of variables not directly recorded in the eCRF. Derived variables will be marked in subject data listings by "#" in the listing header.

7.7.1 Baseline Definition and Change from Baseline

In general, the baseline value of an assessment is defined as the last available measurement before start of treatment. For vital signs (except for height, weight and BMI), physical examination, serum chemistry and automated CBC, baseline is the last available measurement before visit 1 (cycle 1, week 1). For the remaining variables baseline values are collected at the screening visit.

Change from baseline will be calculated as follows only for continuous variables:

Change from baseline = (post-baseline value) – (baseline value)

7.7.2 Transfusion History

Number of units within [redacted] weeks before treatment

The number of units within [redacted] weeks will be defined as the sum of all units of the same type (RBC or platelets) transfused before and including the date of the first IMP administration, i.e., all transfusions dated in the interval [DA [redacted] days, DA [redacted] where:

DA [redacted] = Drug administration date of [redacted] [YYYY-MM-DD]

Number of units after first dose

The number of units after first dose will be defined as the sum of all units of the same type (RBC or platelets) transfused between the date of IMP administration and the date of study discontinuation (SD).

Rates

The respective transfusion rates will be defined as the number of units in each period divided by the number of days in the period, i.e., [redacted] days before treatment and TD [days] = SD - DA [redacted] after first dose.

7.7.3 Duration of treatment

Duration of treatment (DoT, in days) will be defined as the time elapsed from the start of treatment (date of administration at cycle [redacted], week [redacted]) to the date of treatment discontinuation (TD) or the last available date with drug administration (LD):

DA [redacted] = Drug administration date in Visit [redacted] [YYYY-MM-DD]

DoT [days] = min(TD, LD) - DA [redacted]

7.7.4 Hematological response

All patients with one of the following responses assessed by samples and procedures taken/carried out at visit [redacted] in cycle [redacted] are defined as responders (assessed through the combined response criteria for MDS and AML used in this trial (see section 11.2 Appendix 2)):

[1] CR, CRi, PR as defined in section 11.2 Appendix 2 a)

[2] Hematologic improvement (for one or several lines) as defined in section 11.2 Appendix 2 a)

If any of those criteria is fulfilled, the subject will be classified as responder. Otherwise, he will be classified as non-responder. Patients for whom the overall hematologic response cannot be determined will be considered as treatment failures.

7.7.5 Overall Survival

Overall survival (OS, in days) will be defined as the time from the beginning of treatment (date of administration at cycle [redacted], week [redacted]) until date of death or censored at the date of the last observed time point alive:

In case subject dies overall survival will be:

OS [days] = date of death – Drug administration date in Visit [redacted] +1

Otherwise, censoring date will be:

OS [days] = Date of last observed time point alive – date of beginning of treatment +1

7.7.6 Progression-free-survival

Progression-free-survival (PFS) will be defined as the duration of time from time of treatment to time of progression or death, whichever occurs first. A subject who has neither progressed (defined as first time having Progressive disease (PD) or Progression or relapse after HI on response assessment) nor died will be censored on the date of the last observation. Therefore:

In case there was a progression or death:

PFS [days] = min(date of progression/death) – Drug administration date in Visit [redacted] +1

Otherwise, censoring date will be:

PFS [days] = date of last observation – Drug administration date in Visit [redacted] +1

7.7.7 Duration of response

Duration of response (DoR) will be measured from the time measurement criteria are met for CR, CRi, PR, MLFS or SD (whichever is first recorded, defined in section 11.2 Appendix 2 a)) until the first date at which recurrent or progressive disease is objectively documented for patients with confirmed CR, CRi, PR, MLFS or SD criteria met. Therefore:

DoR [days] = first date with PD response criteria after response – date of CR, CRi or PR response criteria +1

If there was no progressive disease documented, subject will be censored on last documented response assessment:

DoR [days] = date of last response assessment – date of CR, CRi or PR response criteria +1

7.7.8 Best overall response

Best overall response will be defined as the best response recorded from the start of the treatment until diagnosis of disease progression. Response hierarchy considered as order of appearance on section 11.2 Appendix 2 a)

7.7.9 Response based on IWG 2023

Response based on IWG 2023 criteria (see Appendix 11.2 b) at visit 9 will be analyzed only for MDS population. Response assessed in week [redacted]) will be classified as:

- Overall Response Rate (ORR) = CR (or CR equivalent)* or PR or CRL or CRh or HI

or

- No response = Not meeting criteria for CR (or CR equivalent)* or PR or CRL or CRh or HI.

by these criteria.

7.7.10 HRQoL scores

Health-Related Quality of Life (HRQoL) score will be accessed using EORTC QLQ-C30, version 3. This questionnaire contains 30 items with different rating scales. Therefore, Table 4 is used to score:

Table 4: Scoring the QLQ-C30 v3.0

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

The scoring of the questionnaire will be based on the manual of the EORTC-QLQ-C30 (https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf)

Mean score of items belonging to the same scale is computed as Raw Score (RS):

$$RS_i = \frac{I_1 + \cdots + I_n}{n}; \quad i = Scale$$

All mean scores will be standardized into a 0 to 100 scale.

For **functional scales** (marked as F in Function scales column), final score (S_i) will be:

$$S_i = \left\{1 - \frac{(RS_i - 1)}{Item\ range}\right\} \times 100; \quad i = Scale$$

For **symptom scales/items** and **global health status/QoL**, final scores will be:

$$S_i = \left\{\frac{(RS_i - 1)}{Item\ range}\right\} \times 100; \quad i = Scale$$

If at least half of the items of a scale are not missing, missing values will not be computed in the average calculation. Otherwise, the score will be stated as missing.

7.7.11 Time to Onset and Duration of Adverse Events

Time to onset of AEs

The following formula will be used to calculate the time to onset of AEs:

Time to onset [days] = start date – date of first treatment +1

This formula can be used analogously whenever the time of onset must be calculated.

Duration of AEs

The following formula will be used to calculate the duration of AEs:

Duration [days] = stop date – start/onset date + 1

This formula can be used analogously whenever the duration must be calculated.

7.7.12 Adverse Event and Toxicity Classification

An adverse event will be classified as a treatment emergent adverse event (TEAE) when it occurs only after 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.

Treatment emergent adverse events will be grouped into related and unrelated TEAEs. All TEAEs that are at least possibly related (Possible related, Probable related, Related) to the treatment or with missing assessment of the relationship will be categorized as related. All other TEAEs will be regarded as unrelated to the treatment.

For the purpose of ranking the severity of an TEAE and the toxicity, the categories will be ordered as following, from lowest to highest severity according to CTCAE v5.0:

- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Life threatening consequences)
- Grade 5 (Death related to AE)

TEAE occurring before visit [redacted]) will be accounted for early toxicity.

7.7.13 Time to first related TEAE with toxicity of grade 3 or higher

The time to first related TEAE with toxicity of grade 3 or higher (TtFRT) will be measured as the difference between the date of first dose administration and the date of the first occurrence of a TEAE classified as related with severity of grade 3 or higher as defined in section 7.7.12. I.e.:

TtFRT [days] = min(Date of TEAE where(severity ≥ 3 and Relationship in (Possible related, Probable related, Related)) - Drug administration date in Visit [redacted]) +1

Otherwise, censoring date will be:

TtFRT [days] = date of last observation – Drug administration date in Visit [redacted]) +1

8. Statistical Analysis Methods

8.1 Descriptive Statistics

The default summary statistics for quantitative variables will be the number of non-missing observations (n) and the number of missing observations (miss) as well as arithmetic mean, standard deviation (STD), minimum (min), median, and maximum (max).

For categorical variables, the number (n) and percentage (%) of subjects per category will be the default summary presentation, and, if applicable, the number of missing values is provided in a "missing" category. For the number of missing values, all subjects in the respective study population will be counted. Percentages will be calculated using a denominator of all subjects in a specified population with non-missing data. If necessary, the denominator will be specified in a footnote to the tables for clarification.

Visit related descriptive statistics will be provided only for visits with more than 5 non-missing observations. Results from visits with 5 or less non-missing observation will be only listed.

8.2 Evaluation of Non-Objective Related Characteristics

8.2.1 Disposition of Subjects

Subject disposition will be tabulated by cohort (see 2.7) including the variables listed in 6.1. Subjects will be allocated on each treatment regimen depending on if they were screened before or after the IA. The analysis will be repeated per site. A flow-chart detailing the number of subjects at the different stages will be prepared. The number and percentage of subjects per visit/cycle will be summarised in a further table. Subjects withdrawn from the study will be listed along with the primary reason for discontinuation. In addition, the primary reason for withdrawal will be tabulated. Exclusion from analysis sets as well as the reason(s) for exclusion will be listed. A table detailing the number of subjects per visit will additionally be provided.

Table	
14.1.1	Subject disposition by site and overall
14.1.2	Visit/cycle attendance
Figure	
14.1.1	Disposition flow chart
Listing	
16.1.1	Informed consent information, Screening failure, Enrolment, Treated

16.1.2	Visit dates and withdrawals
16.1.3	Protocol deviations and other reasons for exclusion from analysis sets, assignment to analysis sets

8.2.2 Demographics and other baseline characteristics

Demographic and baseline characteristics (see section 6.1) will be summarized by treatment cohort (see 2.7) using summary statistics (see section 8.1) for continuous variables (age, ECG) or absolute and relative frequencies (n, %) for categorical variables (Gender, Race, IPSS-R score, WHO Classification). Results will be presented by FAS and, if the analysis sets differ more than 10% between the number of included subjects, will be presented also for the other analysis sets (SES, PPS).

Table	
14.2.1	Demographics and body measurements
14.2.2	Baseline characteristics (continuous)
14.2.3	Baseline characteristics (categorical)
Listing	
16.2.1	Demographics
16.2.2	WHO classification
16.2.3	IPSS-R score
16.2.4	ECG

8.2.3 Medical History, Concomitant Diseases/Procedures, Previous and Concomitant Medication

Absolute and relative frequencies (n, %) of concomitant disease will be summarized based on MedDRA system organ class (SOC) and preferred term (PT) levels for the SES.

Absolute and relative frequencies (n, %) concomitant medication and MDS/AML specific concomitant medication will be summarized based on Anatomical Therapeutic Chemical (ATC) Classification code levels 2 and 3 for the SES.

Absolute and relative frequencies (n,%) of MDS/AML related Medical History will be summarized for the SES.

All results will be presented by cohort (see 2.7).

Table	
14.3.1	Concomitant diseases by SOC and PT
14.3.2	MDS/AML related history
14.3.3	Concomitant medications by ATC levels
14.3.4	MDS/AML specific concomitant Medication by ATC levels
Listing	
16.3.1	Concomitant diseases
16.3.2	MDS/AML related history
16.3.3	Concomitant Medication
16.3.4	MDS/AML specific concomitant Medication
16.3.5	Medical history
16.3.6	Prior MDS/AML specific medication

8.3 Evaluation of Primary Endpoint

The primary objective of this study is to assess the efficacy of imetelstat for the treatment of AML and MDS patients failing or being refractory to first line hypomethylating agent (HMA)-based treatment. This should be illustrated by testing the hypothesis stated in section 2.5 using the primary endpoint stated in section 6.2.1 (see 7.7.4 for derivation).

The absolute and relative frequencies of overall hematological response as assessed in week [redacted] (beginning of [redacted]) of treatment with imetelstat will be evaluated using the FAS and repeated for the PPS if the analysis sets differ more than 10% between the number of included subjects. 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.

The primary analysis will be based on a Simon's two-stage design for an initial assessment of efficacy. Based on the study hypothesis (see section 2.5), an absolute cut-off value of [redacted] subject out of [redacted] will be used to determine if the study must be stopped for futility at the IA. For the final analysis in case the study proceeds, if final sample size is equal to the calculated one, a cut-off value of [redacted] subjects out of [redacted] will be fixed.

If final sample size is different from the calculated sample size (overrunning), uniformly minimum variance unbiased estimator UMVUE will be tested (see Melikov M. & Karanevich A. 2022) with a

model based on a binomial distribution conditioned to the first stage results and with an assumed expected true response rate of 0.2.

A SAS macro (based on source https://www.lexjansen.com/pharmasug/2022/SA/PharmaSUG-2022-SA-123.pdf) can be used for this analysis (see Appendix 11.4)

For the IA:

A binomial exact test will be performed with a two-sided 90% confidence interval for overall hematological response rate using the Clopper-Pearson method. A SAS pseudo code can be:

```
proc freq data=Data;
 tables Hematological_response / binomial(all level="0") alpha=0.1 cl ;
 exact binomial /point;
run;
```

For the final analysis:

The final analysis was going to be performed with a calculation of the p-value and a 90% confidence interval (two-sided, equivalent to a one-sided 95% confidence interval) for the UMVUE (see Melikov M. & Karanevich A. 2022).

[redacted]

Due to the transient improvement seen in WBC and peripheral blasts in patients early in treatment, it was accorded to continue the study in an exploratory approach with a change in dose frequency. Therefore, binomial test will be performed with a two-sided 90% confidence interval for overall haematological response rate using the Clopper-Pearson method for both treatment cohorts (see 2.7) independently. Analysis will be repeated by subgroups (see 4.2). A SAS pseudo code can be:

```
proc freq data=Data;
 by Treatment_cohort;
 tables Hematological_response / binomial(all level="0") alpha=0.1 cl ;
 exact binomial /point;
run;
```

Response assessments of visit 5(W9 C3) and visit 9(W17 C5) will be listed.

Table	
14.5.1	Overall hematological response rate
Figures	
14.5.1	Overall hematological response rate at beginning of cycle 5
Listing	
16.5.1	Response assessment

8.4 Evaluation of Secondary Endpoints

Analyses of secondary endpoints will be performed in exploratory manner based on the FAS.

All results will be presented by treatment cohort (see 2.7).

8.4.1 Overall survival

Overall Survival (OS) as defined in 7.7.5 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] (in [redacted]) and for the overall study data at data hard lock with two-sided 95% confidence intervals (CI) using the complementary log-log transformation method will be tabulated.

The following pseudo-SAS code can be used defining Status = 0 as Censored and Status = 1 as event:

```
proc lifetest data=Data plots=survival(cb=hw test atrisk);
        time OverallSurvival*Status(0);
run;
```

Table	
14.6.1	Overall survival
Figures	
14.6.1	Overall survival

8.4.2 Progression-free-survival

Kaplan-Meier method will be used to assess progression-free survival (PFS) as defined in 7.7.6. Kaplan-Meier Curves depicting PFS will be generated. Additionally, median PFS, PFS rate at week [redacted] (in [redacted]) and for the overall study data at data hard lock will be reported. The two-sided 95% confidence intervals (CI) for the median, and PFS rates will be calculated using the complementary log-log transformation method.

A similar pseudo-SAS code as in 8.4.1 can be used.

Table	
14.6.2	Progression-free survival
Figures	
14.6.2	Progression-free survival

8.4.3 Response related endpoints

Duration of response

Kaplan-Meier method will be used to assess duration of the response (see section 7.7.7 for deviation) will be summarised using descriptive methods described in section 8.1.

Table	
14.6.3	Duration of response

Best overall response

Best overall response (see section 7.7.8) at the end of treatment will be summarized using descriptive methods described in section 8.1. The summary table will include frequencies and percentages for each response category (CR, PR, SD, etc. described in 11.2).

Table	
14.6.4	Best overall response

8.4.4 Response based on IWG 2023

Response based on the updated IWG 2023 criteria at visit 9 will be analyzed only for MDS population. The summary will be based on descriptive methods, as described above.

Table	
14.6.5	Response based on the updated IWG 2023

8.4.5 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 (as defined on 7.7.10) will be summarized with descriptive statistics by visit. Moreover, the sub scores (linear transformation to 0 to 100) will also be provided.

Table	
14.6.6	Health-Related Quality of Life
Listing	
16.6.6	Health-Related Quality of Life

8.5 Evaluation of Safety Endpoints

Analysis of safety endpoints will be based on the SES. Adverse events will be analyzed by relationship (Possible related, probable related and related will be considered as related to IMP) and severity (Grade 3 or higher according to CTCAE v5.0 will be considered as severe).

All results will be presented by treatment cohort (see 2.7).

8.5.1 Analysis of AEs

The analysis of AEs will be based on the SES. In this trial, only TEAE's (see section 7.7.12) will be analyzed. TEAEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

An overview of the subjects experienced an TEAE and the number of TEAE will be tabulated. Additionally, TEAE will be summarized by relation to IMP, toxicity (severity), special interest (AESI) and early toxicity.

Individual listings of AEs, SAEs and deaths will be generated.

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

Table	
14.7.1	TEAEs by SOC and PT, overall
14.7.2	TEAEs by SOC and PT, by relationship
14.7.3	TEAEs by SOC and PT, by toxicity
14.7.4	TEAEs by SOC and PT, by early toxicity
14.7.5	TEAEs by SOC and PT, by special interest
Listing	
16.7.1	Adverse events
16.7.2	Serious adverse events
16.7.3	Adverse Events leading to discontinuation
16.7.4	Death

8.5.2 Time and rate to first related TEAE with toxicity of grade 3 or higher

Time to first related TEAE with toxicity of grade 3 or higher acc. CTCAE v5.0 criteria as defined in section 7.7.13 will be evaluated using Kaplan-Meier method based on the SES. The estimates

obtained are invariably expressed graphically. Median survival time with two-sided 95% confidence intervals (CI) using the complementary log-log transformation method will be tabulated. Survival rate before week [redacted] (in [redacted]) and week [redacted] (in [redacted]) with exact two-sided 95% confidence interval using the Clopper-Pearson method will be provided.

Table	
14.7.6	Time and rate to first related TEAE with toxicity of grade 3 or higher
Figures	
14.7.6	Time to first related TEAE with toxicity of grade 3 or higher

8.5.3 Extent of exposure

Duration of treatment (see 7.7.3), treatment compliance, total dose and dose intensity (see 6.2.3) will be summarized with descriptive statistics overall. Dose intensity will be summarized by cycle and by overall mean in a subject level. Dose modifications will be listed separately.

Table	
14.8.1	Extent of exposure
Listing	
16.8.1	Extent of exposure
16.8.2	Dose modifications

8.5.4 Other safety assessments

Clinical chemistry, vital signs, Automated complete blood count and BM Cytology Assessment (see 6.2.3) will be summarized descriptively by visit (using the visit labelling from the SoA (see 2.4)) for the original data as well as for the difference to baseline (as defined in 7.7.1). Patients with laboratory values outside of the normal reference range at any postbaseline assessment will be listed.

Table	
14.9.1	Clinical chemistry
14.9.2	Vital signs
14.9.3	Automated complete blood count
14.9.4.1	BM Cytology Assessment (continuous)
14.9.4.2	BM Cytology Assessment (categorical)
Listing	
16.9.1	Clinical chemistry

16.9.2	Vital signs
16.9.3	Automated complete blood count
16.9.4	BM Cytology Assessment
16.9.5	CBC with differential
16.9.6	Cytogenetic Analysis
16.9.7	Physical examination

8.6 Other Endpoints

Transfusions as defined under section 6.2.3 will be summarized on a subject level based on the FAS using the methods described in 8.1 by transfusion type and differentiating by within 16 weeks before treatment and after first dose transfusions. Non RBC or Platelet transfusions will only be listed.

All parameters will be listed for all available visits (i.e., screening, FU/ET visit and extension treatment phase included) using the visit labelling from the SoA (see 2.4).

All results will be presented by treatment cohort (see 2.7).

Table	
14.10.1	Transfusion history by type of transfusion
Listing	
16.10.1	Transfusion history by type of transfusion

8.7 Further parameters

ECOG Performance Status as defined in section 6.2.3 will be listed including all available visits (i.e., screening, FU/ET visit and extension treatment phase included) using the visit labelling from the SoA (see 2.4).

Listing	
16.11.1	ECOG Performance Status

8.8 Special Analytical Issues

If multiple analysis sets contain the same number of subjects, the analysis will only be performed for one of these analysis sets. In tables and figures, both analysis sets will be referenced, if applicable.

8.8.1 Unscheduled Visits

Unscheduled visits may be performed, as necessary, to ensure the safety and well-being of subjects. Data from these visits will only be included in the subject listings but not in the statistical analysis tables and figures with the following exceptions:

- AEs
- Concomitant medications

9. Changes in the Planned Analysis

For the final analysis, the possibility of overrunning of the study population is described in the SAP (see section 8.3). This represents no change of the evaluation of the primary endpoint at the final analysis. It is an extension to preplanned analysis.

10. References

1. Melikov M. & Karanevich A. “An Expanded Set of SAS Macros for Calculating Confidence Limits and P-values Under Simon’s Two-Stage Design Accounting for Actual and Planned Sample Sizes.” PharmaSUG 2022-Paper SA-123.
2. Platzbecker, U. *et al.* Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood* (2018) doi:10.1182/blood-2018-06-857102.
3. Simon R. Optimal Two-Stage Designs for Phase II. Controlled Clinical Trials 10:1-10(1989)
4. Platzbecker, U. *et al.* Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood* (2018) doi:10.1182/blood-2018-06-857102.
5. Döhner, H. *et al.* Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* **129**, 424–447 (2017).

11. APPENDICES

11.1 APPENDIX 1

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14.7.3	TEAEs by SOC and PT, by toxicity
14.7.4	TEAEs by SOC and PT, by early toxicity

14.7.5	TEAEs by SOC and PT, by special interest
14.7.6	Time and rate to first related TEAE with toxicity of grade 3 or higher
14.8.1	Extent of exposure
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14.9.4.1	BM Cytology Assessment (continuous)
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14.6.2	Progression-free survival
Safety Endpoints	
14.7.6	Time to first related TEAE with toxicity of grade 3 or higher

Listings	
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16.1.1	Informed consent information, Screening failure, Enrollment, Treated
16.1.2	Visit dates and withdrawals
16.1.3	Protocol deviations and other reasons for exclusion from analysis sets, assignment to analysis sets
Demographics and other baseline characteristics	

16.2.1	Demographics
16.2.2	WHO classification
16.2.3	IPSS-R score
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Medical history/ Medications	
16.3.1	Concomitant disease
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11.2 APPENDIX 2: Combined response assessment criteria for MDS and AML

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 109/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.

11.3 APPENDIX 3: 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)

11.4 Appendix 4: SAS Macro

```
%macro Simon_KC (num_success=, n1=21, n=41, r1=1, rt=5, p0=0.1, n2star=,
x1=, alpha=0.1);
      data pval (keep= umvue cpval calpha p_val ord);
      num1=0;
      denom1=0;
      do X1=max((&r1+1),(&num_success-&n2star)) to min(&num_success,&n1);
            num0=comb(&n1-1, x1-1)*comb(&n2star, &num_success-x1);
            num1=num1+num0;
            denom0=comb(&n1, x1)*comb(&n2star, &num_success-x1);
            denom1=denom1+denom0;
            UMVUE=round(num1/denom1, 0.0001);
            /* output; */
      end;
      /*conditional p-value of stage 2 */
      cpval = round(1-CDF('BINOMIAL', (&num_success-&x1)-1, &p0,
      &n2star), 0.0001);
      /*conditional type I error of stage 2 */
      calpha = round(1-CDF('BINOMIAL', (&rt+1)-(&x1)-1, &p0, &n-&n1),
0.0001);
      /*finding pstar*/
      pstar=round(betainv(cpval, (&rt+1)-&x1, (&n-&n1)-((&rt+1)-&x1)+1),
      0.0001);
      /* function calculating p-value using KC equation (7) */
      p_val=0;
      do X1=&r1+1 to &n1;
```

```
      X2 = (&rt+1) - X1; /*To generalize the macro possible val-ues
      of X2 should be based on rt*/
      pr_x = PDF('BINOMIAL', X1, &p0, &n1)*(1-CDF('BINOMIAL', X2- 1,
      pstar, &n-&n1));
      p_val =round(p_val+pr_x, 0.0001);
      /* output; */
end;
ord=1;
run;

/* A confidence interval and a reasonable point estimate */
data confint (keep= ord p0prime );
p_val=0;
p0prime=0;
do clevel = &alpha/2, 0.5, 1-(&alpha/2);
do while (p_val < clevel) ;
p0prime = p0prime + 0.0001;
/*conditional p-value of stage 2 for each incrementally increasing
p0prime */
cpval = round(1-CDF('BINOMIAL', (&num_success-&x1)-1, p0prime,
&n2star), 0.0001);
/*pstar for each incrementally increasing p0prime */
pstar=round(betainv(cpval, (&rt+1)-&x1, (&n-&n1)-((&rt+1)-&x1)+1),
0.0001);
/* function calculating p-value using KC equation (7)*/
/* KC noted that pstar changes with different p0prime*/
/* the function below is simultaneously evaluated with p0prime and
cor-responding pstar */
      do X1= &r1+1 to &n1;
            X2 = (&rt+1) - X1;
            pr_x = PDF('BINOMIAL', X1, p0prime, &n1)*(1-
            CDF('BINOMIAL', X2-1, pstar, &n-&n1));
            p_val =p_val+pr_x;
            if x1=&r1+1 then p_val=pr_x;
            /* output; */
      end;
end;
ord=1;
output;
end;
run;

proc transpose data=confint out=confint1 (rename=(col1=LCL
col2=MEDIAN col3=UCL) drop=_name_) prefix=col;
var p0prime;
by ord;
run;

data final;
merge pval confint1;
by ord;
run;

proc print data=final (drop=ord) label;
```

```
            title "Proper inference for Simon's Two Stage Design";
            label umvue='UMVUE (Point Estimate)'
                  median='MEDIAN (Point Estimate)'
                  cpval='Conditional P-value'
                  calpha='Conditional Alpha'
                  p_val='Unconditional P-value'
            ;
      var umvue median p_val lcl ucl;
      run;
%mend;
```

Variable	
num_success	Overall number of subjects with successful hematological response
n1	Calculated sample size for stage 1
n	Overall calculated sample size
r1	Cut-off value for stage 1
rt	Overall cut-off value
p0	Level of inefficacy
n2star	Real sample size for stage 2
x1	Number of subjects with successful hematological response at stage 1
alpha	Significance level for computing the confidence interval