Official Title: A Phase Ib/II, Open Label Study of Siremadlin Monotherapy and in Combination With Donor Lymphocyte Infusion as a Treatment for Patients With Acute Myeloid Leukemia Post-allogeneic Stem Cell Transplantation Who Are in Complete Remission But at High Risk for Relapse.

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HDM201/Siremadlin

Clinical Trial Protocol CHDM201K12201

A phase Ib/II, open label study of siremadlin monotherapy and in combination with donor lymphocyte infusion as a treatment for patients with acute myeloid leukemia post-allogeneic stem cell transplantation who are in complete remission but at high risk for relapse.

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List of abbreviations

ADL	Activities of Daily Living
AE	Adverse Event
aGvHD	Acute Graft Versus Host Disease
ALLO-SCT	Allogeneic Stem Cell Transplantation
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATG	Anti-Thymocyte Globulin
AUC	Area Under the Curve
AV	Atrioventricular
BAT	Best Available Treatment
BLRM	Bayesian Logistic Regression Model
BMA	Bone Marrow Aspirate
BMB	Bone Marrow Biopsy
21 CFR	Code of Federal Regulations
CABG	Coronary Artery Bypass Graft
cGvHD	Chronic Graft Versus Host Disease
CI	Confidence Interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
COMB	Combination phase
CONF	Confirmation phase
COVID-19	Coronavirus disease 2019
CR	Complete Remission
CRF	Case Report/Record Form (paper or electronic)
CRi	Complete Remission with incomplete hematological recovery
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
CV	coefficient of variation
DDI	Drug-Drug Interactions
DDS	Dose Determining Set
DILI	Drug-Induced Liver Injury
DLI	Donor Lymphocyte Infusion

DLT	Dose Limiting Toxicity
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EBMT	European Group for Blood and Marrow Transplantation
EBV	Epstein-Barr Virus
EC	Ethics Committtee
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event Free Survival
eGFR	Estimated Glomerular Filtration Rate
ELN	European Leukemia Net
EOS	End of Study
EOT	End Of Treatment
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLT3-ITD	FMS Like Tyrosine Kinase 3- Internal Tandem Duplication
FSH	Follicle Stimulating Hormone
G-CSF	Granulocyte-Colony Stimulating Factor
GCP	Good Clinical Practice
[redacted]	[redacted]
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLDH	Glutamate Dehydrogenase
GRFS	Graft-versus-Host Disease/relapse-free survival
GvHD	Graft versus Host Disease
GvL	Graft-versus-leukaemia
h	Hour
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HDAC	Histone deacetylase
hERG	Human ether-a-go-go-related gene
HHV-6	Human Herpes Virus 6
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
HMA	Hypomethylating agent
HR	Hazard Ratio
HSV	Herpes Simplex Virus
i.v.	intravenous
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDFU	Investigational directions for use
IEC	Independent Ethics Committee
IFN	Interferon-gamma
IL	Interleukin
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IST	Immunosuppressive Therapy
IUD	Intrauterine Device
IUS	Intrauterine System
IWG	International Working Group
LFS	Leukemia- free survival
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
LPLV	Last Participant Last Visit
LUC	Large unstained cells
MAINT	Maintenance phase
MDM2	Murine Double Minute-2
MDS	Myelodysplastic Syndrome
MEC	Minimum Exposure Criteria
MedDRA	Medical dictionary for regulatory activities
MFC	Multiparametric Flow Cytometry
MFD	Matched sibling/family donor
mg	milligram(s)
MHC	Major Histocompatibility Complex
MI	Myocardial Infarction
mL	milliliter(s)
MPAL	Mixed phenotype acute leukaemia
MPN	Myeloproliferative Neoplasm
MRA	Magnetic Resonance Angiography
MRD	Measurable Residual Disease
MRI	Magnetic Resonance Imaging
MUD	Matched Unrelated Donor
MUGA	Multiple gated acquisition
N/A	Not Applicable
N/V	Nausea and/or Vomiting
NGS	Next Generation Sequencing
NIH	National Institutes Health
NOS	Not Otherwise Specified
NTI	Narrow Therapeutic Index

NYHA	New York Heart Association
OS	Overall Survival
p.o.	oral(ly)
PB	Peripheral Blood
PBPK	Physiological based pharmacokinetic modelling
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PD-1	Programmed cell death protein 1
PK	Pharmacokinetic(s)
PLT	Platelets
PoC	Proof of Concept
PT	prothrombin time
PTFU	Post -Treatment Follow-Up
PRIM	Priming phase
QD	Once a day
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
R/R	Relapsed Refractory
RD	Recommended Dose
RFS	Relapse Free Survival
RNA	Ribonucleic acid
SAE	Serious Adverse Event
sAML	secondary Acute Myeloid Leukemia
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
SD	standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
t-AML	Therapy-related AML
T3	Triiodothyronine
T4	Thyroxine
TAM	Transient Abnormal Myelopoiesis
TBIL	Total bilirubin
Tim-3	T cell immunoglobulin and mucin domain 3
TNF	Tumor Necrosis Factor
TRAIL-R	TNF-related apoptosis-inducing ligand receptor
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of Child Bearing Potential

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy).
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant.
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time.
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days).
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day).
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol.
Enrollment	Point/time of participant start the study treatment for the first time in the study. The action of enrolling one or more participants.
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study.
Medication number	A unique identifier on the label of medication kits.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease.
Participant	A trial participant (can be a healthy volunteer or a patient).

Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol.
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant.
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g., as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent (WoC) /	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's rights are described in the corresponding informed consent form.

Amendment 2 (18-Nov-2022)

Amendment rationale

At the time of release of this amendment, no sites have been initiated, and no subject has been screened or received study treatment in this trial.

The main purpose of this amendment is to restrict the participation of the German sites to Part 1 of the study. The protocol will specify that the participating sites in Germany will enroll patients only in Part 1 with siremadlin monotherapy. The German sites are not permitted to enroll patients in Part 2, which includes Donor Lymphocyte Infusion (DLI) in combination with siremadlin.

Changes to the protocol:

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough red font for deletions and red underline for insertions.

- Protocol summary: Updated to clarify that Germany will not participate in Part 2 in the study design section.
- Section 2.1 - Primary safety estimand for dose confirmation siremadlin monotherapy: Handling of remaining intercurrent events updated to withdrawal before completion of cycle 1 with no DLT prior to completing sufficient scheduled safety assessments: such participants will be considered non-evaluable.
- Section 2.1 - Primary safety estimand for combination phase: Handling of remaining intercurrent events updated to remove relapse and start of a new antineoplastic therapy following while-on-treatment estimand to evaluate safety regardless of relapse or start of new antineoplastic.
- Section 2.1 - Primary safety estimand for combination phase: Handling of remaining intercurrent events updated to remove end of combination phase without experiencing DLT: participants will be censored at the last safety assessment in the combination phase
- Section 2.1 - Primary efficacy estimand: Updated to remove “mainly DLI” in the Best Available Therapy (BAT)
- Section 3- Study design: Updated to clarify that enrollment in Part 2 will not be applicable to the participating sites in Germany.
- Section 5.2: Exclusion criteria 20 updated to clarify that QTcF should be collected prior to start of study treatment.
- Section 6.2.2 – Concomitant therapy: Updated to provide a window of when concomitant medications data should be collected.
- Section 6.2.2.1- Permitted concomitant therapy: Updated to clarify that concomitant use of systemic corticosteroids at higher than specified permitted doses is allowed in life-threatening emergencies.
- Section 6.6.2- Guidelines for dose escalation: Updated to clarify that enrollment in Part 2 will not be applicable to the participating sites in Germany.

- Table 6-3- Management of potential interactions of strong CYP3A inhibitors with siremadlin: Updated for consistency to start for with the lowest dose of 10 mg first and end up with the highest dose (eg. 20 mg) to make up total dose per cycle.
- [redacted]
- Table 8-1- Assessment Schedule, Dose confirmation siremadlin monotherapy (Part 1): Updated the footnote# 26 to add the Section 9.1.1.3 to get more details on the collection of disease response status during the survival follow-up visits for more clarity.
- Table 8-2- Assessment Schedule, Overview (Part 2): Updated the footnote# 20 to add the Section 9.1.1.3 to get more details on the collection of disease response status during the survival follow-up visits for more clarity.
- Section 8.3.1- Efficacy -Disease status assessments: Updated to clarify that hematology assessments will be also collected at the dose confirmation phase.
- Table 8-12 - Extended windows (±2hr) for PK collections at 24 hr postdose for more flexibility.
- Table 8-13 - Extended windows (±2hr) for PK collections at 24 hr postdose for more flexibility.
- [redacted]
- Section 9.1.1 Discontinuation from study treatment: Corrected the linked Section to 6.2.3 (Prohibited medications).
- Section 12.4.2: Statistical Model- Updated to add “off time to DLT for the participants in the DDS2” for better clarity.
- Section 12.5.2 - Safety endpoints: Removed “treatment-emergent ≥ grade 3 immune-related adverse events not attributed to GvHD” from the list of separate summaries of adverse events to be provided.
- Section 12.5.3- Pharmacokinetics analyses: the first paragraph has been removed as the details on the pharmacokinetic analyses will be provided in a separate population pharmacokinetic report.
- [redacted]
- Additional minor changes have been made to correct typographical errors.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Amendment 1 (06-Jul-2022)

Amendment rationale

As the release of this amendment, no sites have been initiated, and no subject has been screened or has received study treatment in this trial.

The main purpose of this amendment is to comply with health authority's request to modify the protocol as follows:

- To modify the study design by adding a siremadlin monotherapy dose confirmation part (Part 1) with at least 6 evaluable participants to evaluate the safety and tolerability of siremadlin monotherapy and determine the recommended dose before commencing the treatment strategy part (Part 2), which includes siremadlin/donor lymphocyte infusion (DLI) combination as well as priming and maintenance with siremadlin monotherapy.
- To specify that after the recommended siremadlin dose is determined in Part 1, enrollment in Part 2 will start after obtaining Health Authority's approval as applicable. Enrollment in Part 2 will not be applicable to the participating sites in the United States.
- To implement a larger dose reduction to 20% of siremadlin (instead of 30%) of the total planned dose when administered concomitantly with strong CYP3A inhibitors in the initial treatment cohort(s). Following the first safety review meeting and based on safety and siremadlin total exposure data, this may be changed to a dose reduction to 30% of the planned siremadlin dose with concomitant use of strong CYP3A inhibitors.
- [redacted]
- To clarify that the decision about DLI administration in eligible participants in Part 2 will be at the discretion of the treating investigator per the standard of practice.

In addition, the following notable changes were made:

- [redacted]
- To remove the donor lymphocyte infusion (DLI) from the study treatment tables as it is not considered as Investigational Medicinal Product or Advanced Therapy Medicinal Products (ATMPs).
- To clarify that a drug diary may be provided to the participants to enhance treatment compliance.

Changes to the protocol:

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough red font for deletions and red underline for insertions.

- Protocol summary: Updated to clarify the requirements to be fulfilled before starting Part 2 and combination phase, and changes implement in the body content such as updates from new protocol template where applicable.

[redacted]

- Table 2-1: Secondary [redacted] objectives: the assessment of the effect of study treatment on MRD status after 6 months of study treatment and the exploration of the immunomodulatory effects of siremadlin have been removed. Clarified the objectives and the Part of the study where each objective will be assessed.
- Section 3: Study design modified to add the dose confirmation siremadlin monotherapy (Part 1) and the Part 2 including the 3-part treatment strategy once the siremadlin monotherapy recommended dose is declared. Total number of participants has been updated from 32 to 38. Updated to clarify the requirements to be fulfilled before entering in Part 2 and combination phase where applicable and that enrollment in Part 2 will not be applicable to the participating sites in the United States.
- Figure 3-1: updated with the new study design. Footnotes have been updated to clarify the requirements to be fulfilled before starting Part 2 and combination phase where applicable.
- Section 4.1: Updated to include the Part 2 wording.
- Section 4.2: Updated to further explain the starting dose level at 30 mg/day with siremadlin and the cycle lenght of 42 days in the combination phase versus 28 days in siremadlin monotherapy phase.
- Section 4.3: Updated to clarify that the administration of DLI in combination with siremadlin will be at the discretion of the treating investigator per standard of practice.
- Section 4.5 Risk and benefits: Added the most frequent toxicities with siremadlin and that no potential clinical risk of QT prolongation was identified so far in preclinical studies.

[redacted]

- Section 5.1: Inclusion criteria 3 updated to remove the sentence related to the patient receiving cyclophosphamide since participants are not required to have started or completed IST taper prior to start the study treatment.
- Section 5.1: Inclusion criteria 4 updated to remove the pre-allo-SCT participant with AML in morphologic complete remission at time of transplant but with evidence of residual leukemia.
- Section 5.1: Inclusion criteria 6 updated to clarify that DLI will only be applicable for the participants enrolled in Part 2.
- Section 5.1: Inclusion criteria 8 removed the systemic GvHD prophylaxis or treatment IST taper to be started prior to start of study treatment or has been completed.
- [redacted]
- Section 5.2: Exclusion criteria 4 updated to add that a history of lower grades of GvHD is permitted if GvHD resolved to grade 0 for at least 4 weeks prior to start of study treatment.

- Section 5.2: Exclusion criteria 10 updated to add that prior systemic cancer-directed treatments or investigational modalities ≤ 5 half-lives or 4 weeks prior to starting study, whichever is longer.
- Section 5.2: Exclusion criteria 12 updated to add the cancers treated with hormonal therapy.
- Section 5.2: Exclusion criteria 17 updated to add the new language as per the protocol template version 5.
- Section 5.2: Exclusion criteria number 18 has been added as it was missed in the previous protocol version.
- Section 6.1; Table 6-1; Table 6-6: Removed the Donor Lymphocyte Infusion from the study treatment and Dose and treatment schedule and added in the Additional treatment paragraph.
- Table 6-1: Study treatment table updated to add siremadlin 30 mg as an additional strength.
- Section 6.1.2: Additional study treatment section removed as the supportive care measures have been moved in the Section 6.2 Other treatments. The subsequent subsections have been renumbered (for numbering continuity) due to deletion of Section 6.1.2 Additional study treatments.
- Section 6.1.2 Treatment arms/group: Updated to add the Part 2 study design.
- Section 6.1.3:
  - updated the eligibility criteria for DLI administration in combination with siremadlin to clarify that the participant should not have had Grade II-IV aGvHD (per Harris et al 2016) during priming phase.
  - Clarified the requirements to be fulfilled to enter the combination phase where applicable.
  - Updated the eligibility criteria to clarify that a participant can proceed to maintenance phase if he has no active aGvHD (per Harris et al 2016)
- Section 6.1.4: Treatment duration- Updated to add the dose confirmation siremadlin monotherapy
- Section 6.2.1: Updated to include the DLI text moved from Section 6.1.1.
- Section 6.2.2: Updated to clarify the IST taper schedule and handling.
- Section 6.2.2.1: Strong CYP3A inhibitors: Addition of the dose reduction of siremadlin to 20% of the total planned dose per cycle (reduction level 1) in Table 6-2 and updated the dose reduction of siremadlin to 30% of the planned dose per cycle (reduction level 2) in Table 6-3 when given concomitantly with strong CYP3A inhibitors.
- Section 6.2.3: Updated to add that DLI will not be permitted in study Part 1.
- Section 6.3.1.1: Sentence added to inform that investigators may provide participants with drug diary to facilitate treatment compliance for treatments taken at home.
- Section 6.3.1.2: Moved the donor lymphocyte infusion handling information from Section 6.3.2 to Section 6.3.1.2 [Handling of other treatment].
- Table 6-5: Updated the title to “Timepoints for IST drug level measurements to be recorded by the investigators”.

- Section 6.6.1: Dose escalation guidelines – Updated to add the dose confirmation siremadlin therapy
- Section 6.6.2: Guidelines for dose escalation and determining the recommended dose have been updated to clarify the requirements to be fulfilled before starting Part 2.
- Section 6.6.3: DLT definition updated to add the minimum dose criteria and clarified the adverse events to be notified by the investigator to the Sponsor.
- Section 6.6.4: Updated to clarify the guidelines for dose modifications decision for toxicities (other than GvHD) in Part 1 and Part 2.
- Section 6.7.1: Treatment compliance- Updated to clarify the study treatment to be recorded on the study dispensation form.
- Table 6-8: Criteria for defining dose limiting toxicities- updated to add any adverse event that leads to study treatment discontinuation if not clearly resulting from the underlying leukemia, inter-current illness, or concomitant medications.
- Table 6-9: Dose modification of siremadlin for grade 4 neutropenia and for grade 4 thrombocytopenia was revised. The revision conveys that siremadlin dose reduction by one dose level will occur after the first occurrence of grade 4 neutropenia and/or grade 4 thrombocytopenia. Dose modification of siremadlin for asymptomatic amylase and/or lipase elevation and pancreatitis was clarified.
- Section 7: Updated to include the new wording for the Informed Consent procedures section as per protocol template version 5.
- Section 8: Updated as per protocol template version 5 language.
- Table 8-1: Updated to add for the dose confirmation siremadlin monotherapy visit schedule assessment (Part 1), End of treatment visit, Post-treatment follow-up visit and Survival follow-up visits assessments
- Table 8-2, Table 8-3 and Table 8-4:
  - [redacted]
  - Added additional checks for hematology and chemistry blood collection, and updated to Day 1, 8 and 15 of the first 2 cycles, then Day 1 and 15 of cycle 3 to cycle 6 during the priming phase and on Day 1 and 15 of each combination cycle during the combination phase. Clarified the hematology and chemistry collection during the Post treatment follow-up phase.
  - Updated the IST level measurement collection time and replaced “taper” with “level”.
  - Updated the acute GvHD and chronic GvHD collection time during the maintenance phase (Part 2) and during Post-treatment follow-up phase.

- [redacted]
- Section 8.2: Participant demographics section:
  - updated to add the data collection of prior antineoplastic therapy and allo-SCT characteristics at the screening visit.
  - [redacted]
- Section 8.4.1: Updated to include the new wording from the protocol template version 5.
- Section 8.4.3: Pregnancy and assessment of fertility updated as per protocol version 5.
- Section 8.4.4: Other safety evaluation- Updated to add the dose confirmation siremadlin therapy part 1.
- [redacted]
- Table 8-10, Table 8-12; Table 8-14 and Table 8-16: Added for the dose confirmation siremadlin monotherapy assessments (Part 1).
- [redacted]
- Section 9.1.1.2: Post-treatment Follow-Up- Updated the wording for the withdrawal of consent as per protocol template version 5.
- Section 9.1.1.3: Survival follow-up- Clarified the disease status collection during the survival follow-up period.
- Section 9.2: Clarified the withdrawal of consent language as per protocol template version 5.
- Section 10.1.3: Safety reporting- Updated to include new guidances for the safety reporting timeframes and conditions.
- Section 12.1, Section 12.2 and Section 12.3:
  - Updated to clarify the study treatment phases Part 1 and Part 2 wording.
  - Wording aligned with the objectives in Table 2-1.
- Section 12.4: Analysis supporting primary objectives. – Updated to change the primary efficacy objective only applicable for part 2.
- Section 12.5: Analysis supporting secondary objectives. Updated to add a secondary efficacy objective and endpoint applicable for part 1 [redacted].
- [redacted]
- Section 12.8: Updated to include Part 1 and Part 2 study phases.
- Section 13, Section 13.1 Regulatory and ethical considerations, 13.3 Publication of study protocol and results, Section 13.4 Quality Control and Quality Assurance, Section 13.5 Participant Engagement: Updated to include the language/instructions for Clinical disclosure needs as per protocol version 5
- Section 15: Updated the reference for Stein et al (2022) which was published in March 2022. [redacted]. Removed the reference Schuurhuis et al (2018).
- Additional minor changes have been made to correct typographical errors.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CHDM201K12201
Full Title	A phase Ib/II, open label study of siremadlin monotherapy and in combination with donor lymphocyte infusion as a treatment for patients with acute myeloid leukemia post-allogeneic stem cell transplantation who are in complete remission but at high risk for relapse.
Brief title	A study of efficacy and safety of siremadlin alone and in combination with donor lymphocyte infusion (DLI) in adults with acute myeloid leukemia (AML) who have received allogeneic stem cell transplant (allo-SCT) but are at high risk for relapse.
Sponsor and Clinical Phase	Novartis Phase Ib/II
Investigation type	Drug
Study type	Interventional
Purpose	The primary purpose of this study is to confirm the safe dose and schedule of siremadlin monotherapy and in combination with DLI according to a treatment strategy that consists of three consecutive phases: priming phase with siremadlin monotherapy, followed by combination phase of siremadlin plus DLI in participants eligible to receive DLI, followed by maintenance phase with siremadlin monotherapy. The study is also designed to assess the preliminary efficacy in preventing hematologic relapse in patients with AML who achieved complete remission (CR) or CR with incomplete count recovery (CRi) following allo-SCT but are at high risk for relapse based on the presence of pre-transplant risk factors.
Primary Objective(s)	**Safety Primary Objectives:** • To determine the dose and schedule of siremadlin monotherapy that is tolerable without unacceptable toxicities (recommended dose for the treatment strategy Part 2), measured by incidence of dose-limiting toxicities (DLTs) in Part 1. The primary clinical question of interest is: Can siremadlin be safely administered as monotherapy on Days 1-5 of a 28-day cycle (at the starting dose level of 30 mg QD) to adult participants with AML who are in CR or CRi starting no earlier than ≥ Day 60 after allo-SCT? • To determine the dose and schedule of siremadlin in combination with DLI that is tolerable without unacceptable toxicities (recommended dose for combination), measured by time to DLT- in Part 2. The primary clinical question of interest is: Following the priming phase with at least 2 cycles of siremadlin monotherapy at the Recommended Dose (RD) for Part 2, can siremadlin be safely administered to adult participants with AML at the tolerated dose from the last priming cycle in combination with DLI? **Efficacy Primary Objectives:** • To evaluate the preliminary efficacy of study treatment strategy (siremadlin monotherapy as priming monotherapy and/or maintenance, with or without siremadlin in combination with DLI on prevention of hematologic relapse, measured by the proportion of participants who are alive and maintained CR or CRi with no evidence of hematologic relapse over at least 6 months after start of study treatment strategy (Part 2). The primary clinical question of interest is: Does siremadlin given in a treatment strategy consisting of priming with or without combination and maintenance therapy have activity in preventing hematologic relapse or death (i.e., maintenance of CR/CRi) in adult participants with AML who are in CR/CRi after allo-SCT irrespective of treatment discontinuation?
Secondary Objectives	• To evaluate the preliminary efficacy of siremadlin monotherapy on prevention of hematologic relapse (Part 1- siremadlin monotherapy at the recommended dose for Part 2) • To assess relapse free survival (RFS) (Part 2).

	• To assess cumulative incidence of relapse at 1 year and at 2 years after start of study treatment (Part 1 and Part 2). • To assess overall survival (OS) (Part 2). • To assess safety and tolerability of siremadlin monotherapy (during dose confirmation, priming and maintenance) and in combination with DLI (Part 1 and Part 2). • To assess the proportion of participants stopping study treatment due to GvHD or other adverse events (Part 1 and Part 2). • To assess the incidence of grade III and IV acute graft vs host disease (GvHD), moderate and severe chronic GvHD (Part 1 and Part 2). • To assess GvHD-free/relapse-free survival (GRFS) (Part 1 and Part 2). • To characterize the pharmacokinetics of siremadlin in monotherapy and in combination with DLI (Part 1 and Part 2).
Study design	This is a Phase Ib/II, single arm, open label, multi-center study of siremadlin as monotherapy and in combination with DLI, in adult participants with AML who are in CR or CRi post allo-SCT but are at high risk for relapse based on the presence of pre-transplant risk factors. The study will enroll approximately **38 participants**. This will start with a dose confirmation of siremadlin monotherapy (Part 1) to explore a maximal of 3 dose levels (starting dose 30 mg/day on days 1-5 of a 28-day treatment cycle, with a dose level +1 at 40 mg/day and dose level -1 at 20 mg/day). It is assumed that approximately 12 participants will be enrolled in 2 cohorts to obtain at least 3 evaluable patients in each cohort for a maximum of 24 cycles in total. Once the recommended siremadlin dose is determined in Part 1, enrollment in Part 2 of approximately 26 new participants will start after obtaining Health Authority's approval as applicable. Enrollment in Part 2 will not be applicable to the participating sites in the United States and Germany. Participants enrolled in Part 2 will follow a treatment strategy, which contains siremadlin monotherapy (priming phase), potentially followed by siremadlin in combination with DLI (at the discretion of the treating investigator per standard of practice for participants who are eligible to receive DLI) then maintenance with siremadlin monotherapy for a **maximum of 24 cycles in total**: • A **priming phase** with siremadlin monotherapy (for at least 2 cycles). Participants who are not eligible for the combination phase of siremadlin/DLI may continue priming phase with siremadlin monotherapy. • A **combination phase** of siremadlin in combination with DLI (siremadlin/DLI) for participants who are eligible to receive DLI (up to a total of 3 combination cycles). • A **maintenance phase** with siremadlin monotherapy.
Rationale	Although allo-SCT continues to be the most potent anti-leukemia treatment for AML, relapse after allo-SCT remains unacceptably high and is the main cause of treatment failure (~40%) and death in adults with AML following allo-SCT. Up to 40% of all relapses will occur within the first 6 months post-allo-SCT. There is currently no approved effective treatment available for AML patients with relapsing disease after transplant, and treatment options are very limited with poor outcomes. Therefore, exploring innovative treatment strategies for prevention of early relapse after allo-SCT remains a continuing area of unmet need. Post-transplant maintenance or preemptive strategies to enhance the graft-versus-leukemia (GvL) effect or to eradicate persistent residual disease may offer the chance for AML patients at high risk for relapsing disease for an improved outcome of allo-SCT as a potentially curable treatment. Siremadlin is a novel investigational MDM2 inhibitor with single-agent anti-AML activity as well as potential immunomodulatory effects, which may enhance GvL, reverse immune escape and delay/prevent AML relapse post-allo-SCT. Furthermore, the combination of siremadlin with DLI (strongly supported by preclinical data) may provide synergistic antitumor effects, further enhance the GvL response, and contribute to improving outcomes and successfully prevent relapse after allo-SCT.

Study population	Study population includes adult patients with AML who underwent an allo-SCT and achieved CR or CRi but remain at high risk for relapse post-allo-SCT based on the presence of pretransplant risk factors as detailed in the inclusion criteria. Approximately 38 participants are planned to be enrolled and treated.
Key Inclusion criteria	Signed informed consent must be obtained prior to participation in the study. • Adults ≥ 18 years of age • Participants with AML diagnosis, who underwent one allo-SCT to treat AML and are currently at **≥ Day 60 but no later than Day 120 (≤ Day 120) post allo-SCT**. • **Pre-allo-SCT** - Participants must have any of the following risk factors that put them **at high risk for relapse**: ● AML in first CR (CR1) prior to allo-SCT with one of the following: ● Adverse risk genetic abnormalities per 2017 ELN risk stratification. ● Patients with TP53 mutant AML at diagnosis are eligible if they meet eligibility criteria. ● Therapy-related AML (t-AML). ● Secondary AML (sAML) [AML secondary to antecedent myelodysplastic syndrome (MDS) or AML secondary to myeloproliferative neoplasm (MPN)]. ● AML in second or greater CR (≥CR2) prior to allo-SCT. • **Allo-SCT** must have the following characteristics: ● Unmanipulated/T cell-replete bone marrow or peripheral blood stem cells as a graft source. ● Matched related (family) donor (MFD) or matched unrelated donor (MUD): Human Leukocyte Antigen (HLA) matching of donor and recipient should be at a minimum of 8/8 antigen or allele matched at HLA-A, -B, -C, -DRB1 loci. ● Any conditioning regimen intensity is permitted, the use of anti-thymocyte globulin (ATG) or alemtuzumab or post-transplant cyclophosphamide as a part of conditioning is allowed ● Donor lymphocytes are collected, cryopreserved and available for infusion (DLI), or obtaining donor lymphocytes for DLI is feasible (Part 2 only). • **Post-allo-SCT**, participants must have achieved complete remission (CR) or CR with incomplete count recovery (CRi) with no current evidence of hematologic relapse (bone marrow blasts < 5%; no circulating blasts in the blood; no evidence of extramedullary disease) • Adequate liver function tests (Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN), total bilirubin ≤ 1.5 × ULN) and renal function (estimated Glomerular Filtration Rate (eGFR) ≥ 45 mL/min/1.73 m^2) (within 14 days prior to start of study treatment). • Evidence of adequate engraftment post allo-SCT: Absolute neutrophil count (ANC) ≥ $1.0x10^9$/L, platelet count ≥ $75x10^9$/L, hemoglobin ≥ 8 g/dL (within 14 days prior to start of study treatment).
Key Exclusion criteria	• Prior exposure to Murine Double Minute (MDM)-inhibitor • Active acute GvHD of any grade (per Harris et al 2016) requiring systemic therapy at time of study treatment initiation • Active chronic GvHD of any grade (per National Institutes of Health (NIH) criteria and Jagasia et al 2015) requiring systemic therapy at time of study treatment initiation • Past history of grade III or IV acute GvHD (per Harris et al 2016) and/or past history of moderate or severe chronic GvHD (per NIH criteria and Jagasia et al 2015). History of lower grades of GvHD is permitted if GvHD resolved to grade 0 for at least 4 weeks prior to start of study treatment. • Recipient of allo-SCT from a matched unrelated donor (MUD) with one or more antigen or allele mismatch at HLA-A, -B, -C, -DRB1 locus (HLA matching less than 8/8 antigens) • Recipient of allo-SCT from a haploidentical family donor • Recipients of cord blood transplant as a graft source

	• Prior systemic cancer-directed treatments or investigational modalities ≤ 5 half-lives or 4 weeks prior to starting study, whichever is longer. • Prior systemic AML-directed treatments given at any time after allo-SCT (including DLI) • History of another primary malignancy that is currently clinically significant or currently requires active intervention. Participants who are receiving adjuvant hormonal therapy for breast, prostate or other cancers are eligible • Participants who require treatment with moderate or strong CYP3A inducers within 14 days prior to starting study treatment, or are expected to receive moderate or strong CYP3A4 inducers during the entire study • GI disorders that may prevent the intake and absorption of oral siremadlin (eg, diarrhea, uncontrolled nausea and/or vomiting, Gastrointestinal (GI) bleeding, etc) • Any concurrent severe and/or active uncontrolled bacterial, viral or fungal infection requiring parenteral antibacterial, antiviral or antifungal therapy. Prophylactic antimicrobial use (oral or parenteral) is allowed • Cardiac or cardiac repolarization abnormality, including but not limited to any of the following: ● History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment. ● Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block). ● Baseline QTcF interval > 470 ms. ● Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (New York Heart Association (NYHA) Grade III/IV) • Other concurrent severe and/or uncontrolled medical conditions or serious organ dysfunction or other co-morbidity that, in the opinion of the investigator, predisposes the participant to high risk of noncompliance with the protocol.
Study treatment	• Siremadlin: Daily on Days 1-5 of every cycle. Starting dose level, 30 mg/day (Part 1); dose level +1, 40 mg/day; dose level -1, 20 mg/day. • 28-day cycle as monotherapy [Part 1, Part 2] • 42-day (6-week) cycle during combination phase of siremadlin with donor lymphocyte infusion (DLI) [Part 2]
Treatment of interest	Siremadlin
Efficacy assessments	Disease response assessment will be performed locally by the Investigator according to the European LeukemiaNet (ELN) AML recommendations and International Working Group (IWG) AML response criteria. The efficacy assessments will be done at screening, at regular intervals during treatment and during the follow-up phase for assessment of disease by collecting the below: • Bone marrow aspirate (BMA) • Bone marrow biopsies (BMB) • Hematology • Extramedullary disease assessment [primarily via physical examination, additional evaluation if clinically indicated (imaging, lumbar puncture, tissue biopsy)].
Pharmacokinetic assessments	Pharmacokinetic (PK) samples will be obtained and evaluated in all participants at all dose levels.
Key safety assessments	• Acute GvHD • Chronic GvHD • Adverse events and serious adverse events • Vital signs • Monitoring of laboratory values

	• Eastern Cooperative Oncology Group Performance (ECOG) performance status • 12-lead -electrocardiograms (ECGs)
Other assessments	[redacted]
Data analysis	**Primary safety analysis:** For participants in the Cycle 1 of Part 1 and the entire combination phase, assessing whether siremadlin at the tested dose levels does not lead to an unacceptable level of toxicity (DLTs) when administered alone or in combination with DLI will be based on the estimation of the probability of DLT for participants in the dose determining set for Part 1 (DDS1) and DDS2 for combination phase in Part 2. Dose confirmation of siremadlin as monotherapy (Part 1) will be based on the incidence of DLTs and will be guided by a Bayesian logistic regression model with the standard EWOC. Dose confirmation of siremadlin in combination with DLI (siremadlin/DLI combination phase) in Part 2 will be based on time-to-DLT using Bayesian time to first DLT model with the standard EWOC considering all available information for up to 3 cycles. **Primary efficacy analysis:** The efficacy of study treatment will be based on the proportion of participants remaining in CR/CRi as per investigator assessment for at least 6 months after the start of study treatment, among participants who initiated priming phase at the siremadlin RD for priming with/without DLI (Part 2). Decision criteria for trial success (dual-criterion) are based on proportion of participants who remain in CR/CRi by investigator assessment and are alive at least 6 months after the start of study treatment): Bayesian statistical significance: probability (CR/CRi rate > 40% | data) ≥ 0.975 (the one-sided p-value must be less than 2.5%) (null value), and Clinical relevance: posterior median of CR/CRi rate ≥ 60% (decision value).
Key words	Phase Ib/II, siremadlin, donor lymphocyte infusion (DLI), MDM2, p53, Acute Myeloid Leukemia (AML).

1 Introduction

1.1 Background

Allogeneic stem cell transplantation (allo-SCT) for AML and relapse post-allo-SCT

Allo-SCT continues to be the most potent anti-leukemia treatment for adult patients with high-risk AML. However, AML relapse after allo-SCT remains unacceptably high and is the main cause of treatment failure (~40%) and death in adults with AML following allo-SCT (Thekkudan et al 2020).

According to a recent publication by D'Souza et al 2020, among allo-SCT recipients who died within 100 days, AML relapse was the most common cause of death (27%), followed by organ failure (25%), infection (20%), Graft Versus Host Disease (GVHD) (10%), hemorrhage (5%), graft rejection (2%), and other causes (9%). After day 100, the most common cause of death was relapse (61%), followed by infection (11%), organ failure (10%), GVHD (9%), hemorrhage (1%), graft failure (1%), second malignancy (1%), and other causes (6%).

Most AML relapses after allo-SCT occur early within the first 6 months post-transplant, and survival after early relapse post-allo-SCT is dismal.

Additionally, outcome data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) from 1788 patients with AML who relapsed after allo-SCT showed that median time to post-allo-SCT relapse was 7 months (range, 1 to 177) with 43% of relapses within <6 months, 39% between 6 months-2 years, 8% between 2-3 years, and 10% within ≥ 3 years. Treatment of relapse included chemotherapy alone, donor lymphocyte infusion (DLI) +/- chemotherapy, or second allo-SCT +/- chemotherapy +/- DLI, with subsequent CR rates of 29%. Survival for all patients was 23% at 1 year after relapse; however, 3-year Overall Survival (OS) correlated with time from allo-SCT to relapse with dismal survival with early disease relapse post-allo-SCT (OS 4% for relapses within the 1- to 6-month, 12% for the 6-month to 2-year, 26% for the 2- to 3-year, and 38% for ≥3-year period (Bejanyan et al 2015).

Another retrospective registry study of 263 patients with relapsed AML after allo-SCT with reduced intensity conditioning (RIC) by the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT), showed an estimated 2-year OS from post-allo-SCT relapse was 14%. Overall, 32% of patients achieved complete remission after their primary intervention for relapse, and longer interval between allo-SCT and relapse was the only factor predicting for response (P = 0.003, Hazard Ratio (HR) = 4.86, 95% Confidence interval (CI), 1.70-13.90). In a multivariate model, an interval from allo-SCT to relapse more than 5 months (HR = 0.50, 95% CI, 0.37-0.67, P <0.001), was associated with longer OS. Two-year OS in patients who relapsed at a median of <5 months post-allo-SCT was 7.5%, vs 20.6% in those who relapsed >5 months post-allo-SCT, P <0.001 (Schmid et al 2012).

Prevention of early relapse after transplant remains a continuing area of unmet need, and post-transplant early cellular or pharmacologic maintenance or preemptive strategies to enhance the GvL effect or to eradicate persistent residual disease have been of renewed interest.

Therefore, it is important to identify patients who have a higher risk of relapse after allo-SCT to tailor transplant and post-transplant management strategies with an aim to reduce the relapse incidence, and to offer therapies to patients who would benefit most (Oran et al 2017).

Pre-transplant risk factors and risk of relapse post-allo-SCT

The presence of certain pre-transplant risk factors may identify a patient population with a particularly high risk for relapse rather early after allo-SCT, resulting in poor overall prognosis. These pre-transplant risk factors include but not limited to: (1) AML in first CR (CR1) prior to allo-SCT with either adverse risk (unfavorable) genetic abnormalities per 2017 ELN risk stratification, or therapy-related AML (t-AML), or secondary AML (sAML) [AML secondary to antecedent myelodysplastic syndrome or AML secondary to myeloproliferative neoplasm]; (2) AML in second CR (CR2) or greater prior to allo-SCT; (3) AML in morphologic CR (<5% leukemic blasts) at time of allo-SCT (prior to starting conditioning regimen) but with evidence of residual leukemia (Araki et al 2016, Ganapule et al 2017, Craddock et al 2018, Schmaelter et al 2020, Gilleece et al 2020, Hansen et al 2021).

Allo-SCT for AML in CR1 with adverse risk genetic abnormalities per 2017 ELN risk stratification

A retrospective analysis of 2028 patients who received an allo-SCT between 2000 and 2015 for de novo AML in CR1 showed that adverse risk cytogenetics at diagnosis was one of the overall factors predicting relapse ($p < 0.001$), and was associated with increased risk of relapse following transplant between 3 to 6 months ($p < 0.001$, HR 2.47, 95% CI [1.73–3.51]), 6 to 12 months ($p = 0.003$, HR 1.97, 95% CI [1.26–3.07]), and later relapse > 12 months post-allo-SCT ($p = 0.002$, HR 1.94, 95% CI [1.27–2.97]) (Craddock et al 2018).

Another recent report examined the effect of 2017 European LeukemiaNet (ELN) genetic risk stratification on allo-SCT outcomes of AML in 500 adult patients, in CR1 (n = 370) or CR2 (n = 130), from 2005 to 2016. Patients were classified into favorable (12%), intermediate (57%), and adverse (32%) 2017 ELN risk groups. Patients in the adverse risk group had the highest risk of relapse and worst survival. OS at 2 years was 72%, 60%, and 45%, in the favorable, intermediate and adverse risk group, respectively (p <0.001). In multivariable analyses, the 2017 ELN classifier was an independent predictor of OS after allo-SCT with significantly higher overall mortality in the intermediate (HR = 1.68, 95% CI, 1.06-2.68; $p = 0.03$) and adverse (HR = 2.50, 95% CI [1.54-4.06]; $p < 0.001$) risk groups compared to the favorable risk group. Leukemia- free survival (LFS) was worse in the intermediate (HR = 1.63, 95% CI [1.06-2.53]; $p = 0.03$) and adverse (HR 2.23, 95% CI [1.41-3.54]; $p < 0.001$) risk groups, while relapse was higher in the adverse risk group (HR = 2.36, 95% CI [1.28-4.35]; $p = 0.006$) as compared to the favorable risk group (Hansen et al 2021). The risk of relapse in patients with adverse risk genetics by ELN 2017 risk stratification following allo-SCT in CR1 was estimated to be 45-55% (Loke et al 2020).

Allo-SCT for AML in CR1 secondary to antecedent myelodysplastic syndrome or myeloproliferative neoplasm (sAML) or therapy-related AML (t-AML)

A recent retrospective, EBMT registry-based, analysis of the outcomes of allo-SCT for sAML [AML that evolved from previous myeloid malignancy or therapy-related AML (t-AML)]

[n= 1325, including 825 evolved from previous MDS, MPN, MDS/MPN overlap, others; and 500 t-AML following chemotherapy or radiation for other types of cancer], in comparison to de novo AML (11,439 patients), reported that among transplants in CR1 (n= 8,600), the 3-year cumulative incidence of relapse (RI) was 28.5% for de novo, and 35% for sAML. Three-year overall survival (OS), leukemia-free survival (LFS) and Graft-versus-Host Disease/relapse-free survival (GRFS) was 60.8%, 55.1%, and 38.6% for de novo, and 46.7%, 41.6%, and 28.4% for sAML, respectively. In multivariate analysis, sAML was associated with a lower OS (HR = 1.33 ,95% CI [1.21–1.48]; $p < 10^{-5}$), LFS (HR = 1.32, [95% CI: 1.19–1.45]; $p < 10^{-5}$) and GRFS (HR = 1.2 [95% CI = 1.1–1.31]; $p < 10^{-4}$); and higher RI (HR = 1.27 [95% CI = 1.12–1.44]; $p < 10^{-3}$). Therefore, sAML is identified as an independent risk factor for outcome after allo-SCT in CR1 (Schmaelter et al 2020).

AML in second CR (CR2) or greater prior to allo-SCT

Remission status of CR2 at time of transplant is another significant independent variable for a significantly worse overall survival (HR = 1.49 for CR2 compared with CR1, P = 0.005) (Michelis et al 2015), particularly in patients with shorter duration of CR1 (Gilleece et al 2020).

Beyond CR2 at time of allo-SCT, outcomes are poorer. For CR2 and CR3 status at time of allo-SCT, the 5-year Event Free Survival (EFS) estimate was 49.7% and 33.3%, respectively; and the 5 year OS estimate was 48.2% and 31.2%, respectively (Ganapule et al 2017).

MDM2 inhibitors and immunomodulatory effects

Strong immunomodulatory effects of upregulated, functional p53 have been recently described in murine syngeneic solid cancer (Fang et al 2019, Wang et al 2021) and AML models treated with MDM2 inhibitors including siremadlin. Such immunomodulatory effects of siremadlin could be implemented in order to prevent relapses in AML patients who underwent allo-SCT. In this clinical setting, immune escape mechanisms, such as downregulation of the major histocompatibility complex (MHC)-II as well as pro-apoptotic receptors including Tumor Necrosis Factor (TNF)-related apoptosis-inducing ligand receptor (TRAIL-R-1 and TRAIL-R-2, may promote relapse via evasion from the attack of alloreactive donor T cells post- allo-SCT (Christopher et al 2018, Zeng et al 2014). Preclinical murine data of AML models showed that MDM2 inhibition upregulates the expression of MHC-II and TRAIL-R1/2 in a p53-dependent manner, which consequently may enhance the anti-leukemia immunity post-allo-SCT and reverse immune escape. Furthermore, MDM2 inhibition synergized with the allogeneic immune response and increased the vulnerability of AML cells to allogeneic donor T-cells with improved long-term survival of leukemia-bearing mice when T-cells were combined with MDM2 inhibition. In addition, MDM2 inhibition promoted the cytotoxicity and longevity of the allogeneic donor CD8+ T cells as demonstrated by increased expression of the anti-tumor cytotoxicity markers (perforin, CD107a, IFN-γ, TNF and CD69), which resulted in long-term control of leukemia in murine models (Nguyen Huong Giang Ho et al, in preparation, confidential data on file). These findings suggest that MDM2 inhibition in combination with DLI may provide a therapeutic synergism and enhance graft-versus-leukemia (GvL) effects by augmenting allo-reactive immunity against leukemic blasts after allo-SCT.

Graft-versus-leukemia (GvL)

The aim of allo-SCT is to impose a graft-versus-leukemia (GvL) response of sufficient breadth and depth to eliminate all remaining malignant cells. However, early progression or relapse may occur because GvL responses are nonexistent or insufficient in extent to arrest rapid growth kinetics of malignant cells. This unfortunate phenomenon might be a consequence of T cell depletion as GvHD prophylaxis or intrinsic defects in T or NK cell function or survival (eg, through exhaustion or apoptosis) (O'Neill and Chakraverty 2021). In addition, relapse may occur via immune escape mechanisms, such as downregulation of MHC-II and pro-apoptotic receptors including TRAIL-R1 and TRAIL-R2, which promote AML relapse via evasion of the allogeneic T cells.

Maintenance treatments may be an effective strategy to provide early leukemia control and immunomodulatory support for the GvL effect provided by allogeneic immune responses in patients with high-risk AML. While some strategies focus on the enhancement of GvL, others aim to suppress early tumor progression before GvL is established or are designed to promote antitumor immunity (Burchert et al 2020).

The hypothesis that pharmacological intervention, such as with siremadlin, in the early post-transplant period can modulate the kinetics of disease relapse by providing early leukemia control and suppressing early progression before GvL is well established.

Additionally, such intervention may provide an immunomodulatory support for the GvL effect and enhancement of the effect provided by allogeneic immune responses.

Conceptually, there are a number of mechanisms by which adjunctive post-transplant therapies might reduce the risk of disease recurrence. Firstly, drugs with inherent anti-leukemic activity may simply augment the anti-tumor activity of the transplant.

Secondly, the modulation of the kinetics of disease relapse may give the emerging allo-immune effect a competitive advantage, buying time for the establishment of a clinically significant GvL effect, prior to disease relapse. Thirdly, postponement of disease relapse can in principle permit delaying the administration of DLI until such time that the risk of severe GvHD is reduced. Finally, post-transplant pharmacological therapies may directly modify the allo-reactive response, potentially through up-regulation of tumor antigens or acceleration of T cell reconstitution (Loke et al 2020).

SORMAIN, a placebo-controlled study of FM-like tyrosine kinase 3- internal tandem duplication (FLT3-ITD-targeted maintenance therapy with sorafenib with more than 4.5 years of median follow-up provided evidence that post-allo-SCT maintenance therapy can reduce the risk of relapse and death [HR for relapse or death in the sorafenib group vs placebo group was 0.39 (95% CI, 0.18 to 0.85; log-rank P = 0.013). Of note, 63% of the patients in the sorafenib group were either not in hematologic CR or were not in molecular remission at the time of allo-SCT, which is strongly predictive of poor survival. However, the relapse rate was only 15% after 2 years in the sorafenib arm, which appeared to be a clinically meaningful improvement (Burchert et al 2020).

With Murine Double Minute-2 (MDM2) inhibition, preclinical murine data showed upregulation of MHC-II and the pro-apoptotic receptors TRAIL-R1/2 expression, which may reverse immune escape and enhance the anti-leukemia immunity post-allo-SCT

(Nguyen Huong Giang Ho et al, in preparation, confidential data on file) (see background section).

Donor lymphocyte infusion (DLI) post-allo-SCT

While DLI has more limited efficacy in treating relapsed post-transplant AML, prophylactic DLI may contribute to improving outcomes in high risk AML and may successfully prevent relapse after allo-SCT. DLI has been found to increase anti-leukemic T cells, but also reverses T cell exhaustion through increased IFN-γ production and reduced T cell inhibitory receptors, such as programmed cell death protein 1 (PD-1) and T cell immunoglobulin and mucin domain 3 (Tim-3) (Liu et al 2018, Sterling and Webster 2020).

A registry-based matched-pair analysis in adults receiving DLI in CR vs pair-matched controls for age, diagnosis, cytogenetics, stage, donor, gender, conditioning and T-cell depletion, demonstrated that among patients with high-risk AML (unfavorable cytogenetics and/or transplanted beyond first CR), prophylactic DLI recipients had a significantly improved 5-year OS [69.8% vs. 40.2% among controls; P = 0.027, HR = 0.387, 95% CI (0.116–0.898)] (Schmid et al 2019).

Another retrospective analysis reported the outcomes of DLI after allo-SCT in a cohort of 46 patients for high-risk AML (as defined by cytogenetic aberrations according to the ELN criteria and/or stage of the disease at transplant), compared to a matching control cohort of 34 patients with similar disease characteristics, selection criteria and treatment characteristics (without DLI). The estimated OS from transplantation among DLI recipients at 4 and 7 years were 78% and 67%, as compared with 34% and 31% in the control group (P <0.001). Ten patients (22%) have relapsed despite DLI, as compared with 53% in the control group (P = 0.004). The 6-year LFS was 68% after first DLI as compared with 38% in the control group (P = 0.011) (Jedlickova et al 2016).

Synergism of DLI in combination with pharmacologic approaches

The combination of DLI with novel agents is based on the assumption of synergistic antitumor effects without adding toxicity. Several phase II trials have demonstrated that targeted agents are compatible with immunosuppressive therapy, such as calcineurin inhibitors, which typically precludes simultaneous use of DLI. This opens a window of opportunity during the 4-6 weeks after allo-SCT for the administration of agents that are expected to delay leukemic cell outgrowth at a time when GvL effects are likely to be marginal. Furthermore, although most of these agents are not perfectly tolerated after allo-SCT, maintaining a therapeutically relevant dosage is usually possible, and toxicities are rapidly reversible on interruption (Schmid et al 2021).

The combination of DLI with pharmacologic agents with immunomodulatory effects may enhance antitumor effects of DLI and/or reduce GvHD. Examples are hypomethylating agent (HMA) and histone deacetylases (HDAC) inhibitors, which increase T cell response by upregulated expression of epigenetically silenced tumor antigens, minor histocompatibility antigen, or HLA antigens on malignant cells (render malignant cells more visible for cytotoxic T cells).

Convincing data supporting the combination of DLI with a novel agent came from a retrospective study evaluating salvage therapy with the multikinase inhibitor sorafenib for post-transplantation relapse of FLT3-ITD mutant AML. The subgroup of patients who received DLI in addition to sorafenib benefitted most and achieved a 3-year OS of 40%. Mechanistic analyses showed that sorafenib stimulatedInterleukin-15 (IL-15) production in the FLT3-ITD leukemic cells in responding patients, resulting in metabolic reprogramming and activation of leukemia-reactive CD8 donor αβ T cells (Mathew et al 2018), (Burchert et al 2020).

Furthermore, preclinical data from murine AML models showed that MDM2 inhibition synergized with the allogeneic immune response and increased the vulnerability of mouse and human AML cells to allogeneic T-cells. In leukemia-bearing mice treated with allo-SCT using bone marrow (BM) alone or in combination with T-cells, the addition of T-cells to the allogeneic BM graft improved survival. Treatment with MDM2-inhibitor in the absence of donor T-cells improved survival,but did not lead to long term protection. Only when T-cells were combined with MDM2-inhibition, > 80% of mice were protected long-term. The T-cell/MDM2-inhibitor combination did not increase acute GVHD severity compared to T-cells/vehicle. In addition, MDM2 inhibition promoted the cytotoxicity and longevity of the allogeneic donor CD8+ T cells as demonstrated by increased expression of the anti-tumor cytotoxicity markers (perforin, CD107a, Interferon Gamma (IFN-γ), TNF and CD69), which resulted in long-term control of leukemia in murine models. (Nguyen Huong Giang Ho et al, in preparation, confidential data on file).

1.2 Purpose

This phase Ib/II study is designed to confirm a safe dose and schedule of siremadlin monotherapy and in combination with donor lymphocyte infusion (DLI) [according to a treatment strategy that consists of three consecutive phases: priming phase with siremadlin monotherapy, followed by combination phase of siremadlin plus DLI in participants eligible to receive DLI, followed by maintenance phase with siremadlin monotherapy] (for details, see Section 3).

The study is also designed to assess the preliminary efficacy in preventing hematologic relapse in patients with AML who achieved complete remission (CR) or CR with incomplete count recovery (CRi) following allogeneic stem cell transplantation (allo-SCT) but are at high risk for relapse based on the presence of pre-transplant risk factors.

In adults with AML who have received allo-SCT, the risk of relapse remains unacceptably high and is the main cause of treatment failure (~40%) and death (Thekkudan et al 2020).

There is currently no approved effective treatment available for AML patients with relapsing disease after transplant, and treatment options are very limited and include best supportive care or palliative options, rapid withdrawal of immunosuppression, low or high-intensity chemotherapy followed by cellular immunotherapy, such as a second allo-SCT in selected cases or donor lymphocyte infusion (DLI). However, outcomes following these salvage treatments are generally poor and the majority of these patients eventually succumb to their disease.

Therefore, exploring innovative treatment strategies early post allo-SCT may offer the chance for AML patients at high risk for relapsing disease for an improved outcome of allo-SCT as a potentially curable treatment. Of note, as more than 40% of relapses occur within the first 6

months post-allo-SCT, initiating therapy as early as possible after allo-SCT may be most effective (Bejanyan et al 2015).

Thus far, there are no approved maintenance or preemptive therapies available for AML patients after allo-SCT, and few drugs are being used off-label and per local clinical practice guidelines in this setting in some regions (Heuser et al 2020, National Comprehensive Cancer Network (2021)).

Patients with pre-transplant risk factors that increase the risk of AML relapse following allo-SCT [such as adverse risk genetics at diagnosis, secondary or therapy-related AML, remission status of CR2 or greater at time of transplant, presence of residual leukemia prior to transplant (further details in Section 1.1)] represent the target population that would benefit most from post-transplant interventional strategies. Although the precise risk of relapsing AML post allo-SCT is difficult to assess in this high-risk AML population, it might very well exceed 60% according to most recent interactions with external medical experts.

Among AML patients with high-risk cytogenetic abnormalities treated with allo-SCT, TP53-mutation status has a negative impact on outcomes with significantly inferior overall survival and event-free survival (Middeke et al 2016).

Published reports indicate that prophylactic DLI may reduce or delay relapse in TP53 mutant AML patients (Gao et al 2019, Zhang et al 2021).

In study CHDM201K12201, the eligibility will be independent of the TP53 mutational disease status prior to transplant. This is based on the hypothesis that siremadlin will have direct immunmodulatory effects on leukemic blasts (e.g., upregulation of MHC class II molecules) but also on lymphocyte subsets of the immune microenvironment of leukemic blasts. The TP53 activation mediated by MDM2 inhibition promotes antitumor immunity in the tumor microenvironment regardless of the TP53 status of the tumor. This effect may be related to P53 activation in TP53-non-mutated immune cells in the tumor microenvironment, even in case the infiltrating cancer cells harbor TP53 gene mutations (Fang et al 2019).

Combining DLI with siremadlin may elicit immunomodulatory, potentially curative graft-versus-leukemia (GvL) effects even against AML blasts with non-functional p53 via facilitating GvL-supportive immunologic reactions (activation of GvL-specific allo-reactive donor T cells including DLIs, or other immune cell subsets e.g., via cytokine (IL-15) release to the tumor microenvironment).

Furthermore, as AML is a polyclonal disease, even in patients who had previously been diagnosed with TP53 gene-mutated AML clones, it remains unclear at time of transplant and with the clinical status of CR, whether relapsing AML would exclusively harbor TP53 gene mutations or, more likely, whether at least some of the relapsing clones would actually feature non-mutated TP53 genes and additional genetic features via clonal evolution. In such scenario, the proposed siremadlin/DLI treatment could possibly elicit a strong GvL response against TP53 gene non-mutated leukemic blasts that could be associated with a cross-over GvL effect even against TP53 gene-mutated leukemic blasts.

Taken together, this patient population at high risk to develop relapsing AML after allo-SCT, based on the aforementioned pre-transplant risk factors, is suitable to participate in this study to explore an innovative treatment strategy including early initiation of siremadlin therapy after transplant to prevent relapsing AML.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● **Safety**: ● To determine the dose and schedule of siremadlin monotherapy that are tolerable without unacceptable toxicities (recommended dose for Part 2) [Part 1 - siremadlin monotherapy]. ● To determine the dose and schedule of siremadlin in combination with DLI that are tolerable without unacceptable toxicities (recommended dose for combination) [Part 2 - siremadlin/DLI treatment strategy].	● Incidence of DLTs with siremadlin monotherapy in dose confirmation [Part 1] ● Time to DLT with siremadlin/DLI in combination phase [Part 2]
● **Efficacy**: ● To evaluate the preliminary efficacy of study treatment strategy (siremadlin monotherapy, as priming and/or maintenance, with or without siremadlin in combination with DLI)) on prevention of hematologic relapse [Part 2 – siremadlin/DLI treatment strategy].	● Proportion of participants who are alive and maintained CR or CRi with no evidence of hematologic relapse over at least 6 months after start of study treatment strategy (siremadlin monotherapy, as priming and/or maintenance, with or without siremadlin in combination with DLI) [Part 2].
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To evaluate the preliminary efficacy of siremadlin monotherapy on prevention of hematologic relapse [Part 1 - siremadlin monotherapy at the recommended dose for Part 2].	● Participants who are alive and maintained CR or CRi with no evidence of hematologic relapse over at least 6 months after start of siremadlin monotherapy [Part 1 - siremadlin monotherapy at the recommended dose for Part 2].
● To assess relapse free survival (RFS) [Part 2].	● Time from start of study treatment to the date of first documented hematologic relapse or death due to any cause, whichever occurs first
● To assess cumulative incidence of relapse at 1 year and at 2 years after start of study treatment [Part 1, Part 2].	● Cumulative incidence of AML relapse at 1 year and at 2 years after start of study treatment
● To assess overall survival (OS) [Part 2].	● Time from start of study treatment to the date of death from any cause.
● To assess safety and tolerability of siremadlin monotherapy (during dose confirmation; priming and maintenance) and in combination with DLI [Part 1, Part 2].	● Incidence and severity of AEs and SAEs, changes in laboratory values and vital signs.
● To assess the proportion of participants stopping study treatment due to GvHD or other adverse events [Part 1, Part 2].	● Proportion of participants with permanent discontinuation of study treatment due to GvHD or other adverse events.

Objective(s)	Endpoint(s)
● To assess the incidence of grade III and IV aGvHD, moderate and severe cGvHD [Part 1, Part 2].	● Incidence of treatment emergent grade III or grade IV aGvHD. Incidence of treatment emergent moderate to severe cGvHD.
● To assess GvHD-free/relapse-free survival (GRFS) [Part 1, Part 2].	● Time from start of study treatment to the date of first documented occurrence or worsening of treatment emergent grade III or IV aGvHD, cGvHD requiring initiation of systemic immunosuppressive treatment, occurrence of disease relapse, or death due to any cause, whichever occurs first.
● To characterize the PK of siremadlin in monotherapy and in combination with DLI [Part 1, Part 2].	● Pharmacokinetic parameters (e.g., AUC, Cmax, Tmax) and concentration vs time profiles of siremadlin in monotherapy and in combination with DLI.
[redacted]	

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g premature discontinuation of treatment).

Primary safety estimands:

Dose confirmation siremadlin monotherapy (Part 1):

The primary clinical question of interest is: Can siremadlin be safely administered as monotherapy on Days 1-5 of a 28-day cycle (at the starting dose level of 30 mg QD) to adult participants with AML who are in CR or CRi starting no earlier than ≥ Day 60 after allo-SCT?

The justification for the primary safety estimand is that we wish to determine whether siremadlin leads to unacceptable level of toxicity [Dose Limiting Toxicity (DLT)] when administered as monotherapy in Part 1 and determine the siremadlin recommended dose (RD) for Part 2 as monotherapy.

The primary estimand of safety for dose confirmation is described by the following attributes:

1. Population: Adult participants with AML who are in CR/CRi after allo-SCT and meet eligibility as defined by the inclusion/exclusion criteria.
2. Primary variable: DLT between first dose of siremadlin until end of Cycle 1. Any DLT from participants who initiated siremadlin during Cycle 1 will be considered.
3. Treatment of interest: Siremadlin monotherapy.
4. Handling of remaining intercurrent events:
    - Dose modifications, dose interruptions or discontinuations due to reasons other than DLT leading to less than minimum exposure: such participants will be considered non-evaluable. (Section 6.6 and Section 12.1)
    - Withdrawal from study before completion of cycle 1 with no DLT prior to completing sufficient scheduled safety assessments: such participants will be considered non-evaluable.
5. The summary measure: incidence of DLTs.

Combination phase:

The primary clinical question of interest is: Following the priming phase with at least 2 cycles of siremadlin monotherapy at the RD for Part 2, can siremadlin be safely administered to adult participants with AML at the tolerated dose from the last priming cycle in combination with DLI?

The justification for the primary safety estimand of combination phase is that we wish to determine whether siremadlin in combination with DLI leads to an unacceptable level of toxicity (DLT) when administered after priming phase and determine the siremadlin maximum recommended dose (RD) for combination considering the time to first DLT, dose and schedule.

The primary estimand of safety for combination phase is described by the following attributes:

1. Population: Adult participants with AML who completed at least 2 cycles of priming phase and meet combination phase eligibility to receive DLI as defined in Section 6.1.4.
2. Primary variable:

   Time-to-DLT, defined as time from start of combination phase to first DLT observed during the entire combination phase.
3. Treatment of interest: Siremadlin, at the dose tolerated in the last cycle of priming phase, in combination with DLI (Section 6.1, Section 6.3.2).
4. Handling of remaining intercurrent events:
   - Dose modifications, dose interruptions or discontinuations due to reasons other than DLT leading to less than minimum exposure (details in Section 6.6):
     - Participants who do not satisfy at least one cycle of minimum exposure and do not experience a DLT will be considered non-evaluable.
     - Participants who satisfy at least one cycle of minimum exposure will be censored at the last safety assessment at the end of the last cycle where minimum exposure to study treatment was satisfied. E.g., for a participant who received 2 cycles of combination therapy without any DLT and only met the minimum exposure for the first cycle, this participant will be censored at the end of the first cycle.
   - Death (not caused by study treatment) or withdrawal from study without experiencing DLT: participants will be censored at the last safety assessment at the end of the last cycle preceding death or withdrawal from study (while-on-treatment).
5. The summary measure: probability of DLT

Based on safety/tolerability outcomes of siremadlin/DLI combination, the study may identify a siremadlin maximum RD for combination.

Primary efficacy estimand:

The primary clinical question of interest is: Does siremadlin given in a treatment strategy consisting of priming, combination and maintenance therapy have activity in preventing hematologic relapse or death (i.e., maintenance of CR/CRi) in adult participants with AML who are in CR/CRi after allo-SCT irrespective of treatment discontinuation?

The justification for the primary efficacy estimand is that we wish to estimate the effect of the study treatment and to assess it in the context of published data (included in the dual-criterion for efficacy assessment; more details in Section 12.8.1) of the same patient population treated with Best Available Therapy (BAT), in preventing early relapse of AML post-allo-SCT. The activity of siremadlin is assessed based on the absence of hematologic relapse (maintenance of CR/CRi), which is the most clinically meaningful endpoint in this post-transplant setting (CRi is also acceptable as complete hematologic recovery may be delayed early post-transplant (Dominietto et al 2001)). Patients requiring new antineoplastic therapy (including a second allo-SCT) before completing 6 months after start of study treatment are considered as failure to study treatment. Similarly, withdrawing consent before completing 6 months after start of study treatment could also be attributed to effects of the study treatment and are considered as failure. Discontinuation of study treatment due to other criteria or dose modification might not preclude maintenance of CR/CRi. Medical care of this life-threatening condition is provided also in the

context of a pandemic. The primary estimand will therefore assess the treatment effect regardless of any impact by a pandemic.

The primary estimand of efficacy is described by the following attributes:

1. Population: Adult participants with AML who are in CR/CRi after allo-SCT and meet priming phase eligibility as described in the inclusion/exclusion criteria who initiated priming phase at siremadlin RD for Part 2.
2. Primary variable: CR/CRi per investigator assessment after completing 6 months from start of study treatment. Participants who die, relapse, start new antineoplastic therapy or withdrawal of consent prior to completing 6 months after start of study treatment will be considered as non-responders. (Döhner et al 2017,Cheson et al 2003).
3. Treatment of interest: Siremadlin starting as priming monotherapy for at least 2 cycles, followed by combination of siremadlin with DLI for eligible participants, and then siremadlin monotherapy for maintenance.
4. Handling of remaining intercurrent events:

- Dose modification or treatment discontinuation due to any reason: All assessments will be taken into account regardless of any treatment interruption, dose adjustment or permanent discontinuation (treatment policy strategy).
- Any Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster: All assessments will be taken into account regardless of any disruptions resulting from public health emergencies (refer to Section 4.6) (treatment policy strategy)

5. The summary measure: Proportion of participants who maintained CR or CRi after at least 6 months from start of study treatment and its 95% confidence interval.

2.2 Secondary estimands

Not applicable.

3 Study design

This is a Phase Ib/II, single arm, open label, multi-center study of siremadlin as monotherapy and in combination with Donor Lymphocytes Infusion (DLI), in adult participants with AML who are in complete remission (CR) or CR with incomplete count recovery (CRi) post allo-SCT but are at high risk for relapse based on the presence of pre-transplant risk factors (as specified in Inclusion Criteria Section 5.1).

The study will enroll approximately 38 participants and will start with the dose confirmation of siremadlin monotherapy (Part 1) followed by a treatment strategy with siremadlin/DLI (Part 2) (Figure 3-1):

- **Part 1- Dose confirmation siremadlin monotherapy**: using siremadlin as a single agent, to explore a maximal of 3 dose levels (starting dose 30 mg/day on days 1-5 of a 28-day treatment cycle, dose level +1 at 40 mg/day and dose level -1 at 20 mg/day). It is assumed that approximately 12 participants will be enrolled in 2 cohorts to obtain at least 3 evaluable participants in each cohort. Based on the observed DLT rate, overall safety, tolerability, available PK (and preliminary efficacy) data generated, the participating investigators and

Novartis Team will make decisions regarding the siremadlin dose to be given to participants in the next cohort(s), as guided by a Bayesian Logistic Regression model (BLRM). A minimum of 6 evaluable participants are required to confirm the siremadlin monotherapy dose level that will be declared as the recommended dose for Part 2.

- For each dose level, once the required number of evaluable participants has been confirmed, enrollment will be held until participants have completed the DLT observation period of one treatment cycle. Nevertheless, each participant will continue treatment at his/her tolerated siremadlin dose.
- DLI in combination with siremadlin will not be permitted on study for participants in dose confirmation Part 1. Each participant treated in these dose confirmation cohorts (Part 1) will continue with siremadlin monotherapy for the entire duration of treatment (up to a maximum of 24 cycles).

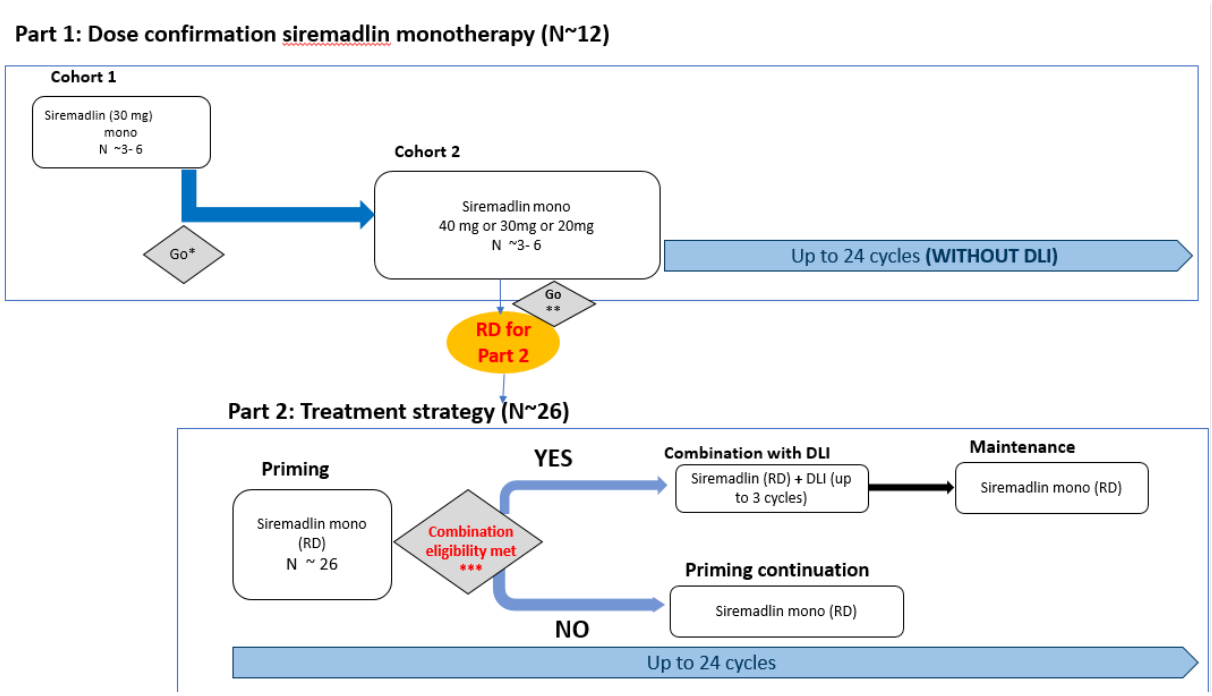
Once the recommended siremadlin dose is determined in Part 1, enrollment in Part 2 will start after obtaining Health Authority's approval as applicable. Enrollment in Part 2 will not be applicable to the participating sites in the United States and Germany.

- **Part 2** - Treatment strategy (siremadlin/DLI): will enroll approximately 26 participants and will not start until the recommended dose for Part 2 is confirmed. Participants enrolled in Part 2 will follow a treatment strategy, which contains siremadlin monotherapy (priming phase), potentially followed by siremadlin in combination with DLI then maintenance with siremadlin monotherapy (as shown in Figure 3-1):
  - A **priming phase** with siremadlin monotherapy. Participants will be administered siremadlin orally on Days 1-5 of a 28-day cycle (for at least 2 cycles). Participants who are not eligible for the combination phase of siremadlin/DLI may continue priming phase with siremadlin monotherapy for up to a maximum of 24 cycles.
  - A **combination phase** of siremadlin in combination with DLI (siremadlin/DLI) for participants who are eligible to receive DLI (up to a total of 3 combination cycles). Criteria to start DLI/siremadlin combination phase are detailed in Section 6.1.4. Participants will be administered siremadlin orally on Days 1-5, at the dose that was received and tolerated in the last cycle of priming phase, in combination with DLI on Day 3 of every 42-day (6-week) cycle (see Section 6.3.2 for details of DLI starting dose and ramp-up dosing instructions).
  - A **maintenance phase** with siremadlin monotherapy. After completion of siremadlin/DLI combination phase, participants may enter maintenance phase with siremadlin monotherapy orally on Days 1-5 of a 28-day cycle starting at the dose that was tolerated in the last cycle in combination phase (refer to Section 6.1.4 for eligibility for maintenance phase).

Intraparticipant dose escalation is not allowed in the trial: each participant will keep his/her allocated siremadlin dose throughout the treatment phases, provided it is well tolerated by the participant (dose modifications are allowed in case of toxicity, see Section 6.6.4).

Study treatment will be administered for up to a maximum of 24 cycles in Part 2 (including priming phase, with or without combination phase, and maintenance phase) or until a participant experiences hematologic relapse, unacceptable toxicity, or withdrawal of consent, whichever is earlier.

Figure 3-1 Study design



* Criteria to proceed with siremadlin dose increase or decrease or Go/No Go for the next Cohort (s): based on incidence of DLTs during the first cycle of study treatment in Cohort 1.

** Go criteria to start treatment in Part 2 at the recommended dose (RD) for Part 2 determined based on incidence of DLTs during the first cycle of study treatment in Cohort 2, after obtaining Health Authority's approval as applicable. Enrollment in Part 2 will not be applicable to the participating sites in the United States and Germany.

*** The decision of DLI administration will be at the discretion of the treating investigator per standard of practice/institutional guidelines; however, participant must fulfill the combination phase eligibility criteria after completion of at least 2 cycles of priming.Safety, tolerability, available PK (if applicable) outcomes of siremadlin in combination with DLI will be analyzed in all participants (refer to Section 6.6.2 for evaluability criteria) when they complete at least the first cycle in combination phase. A Time-to-(first) DLT approach will be used to continuously assess the safety of the combination in individual participants and decide the maximum dose of siremadlin for combination phase. Afterwards participant entering the combination phase must be treated at a siremadlin dose not exceeding the maximum dose for combination. The maximum recommended dose for siremadlin/DLI combination will be declared after all evaluable participants have completed combination phase, and requires a minimum of 9 evaluable participants. Enrollment will not be held for safety assessment of the combination phase.

Safety and tolerability data from all participants in combination phase will continue to be monitored on an ongoing basis following the same approach. (refer to Section 6.6.2 for details)

Study Flow

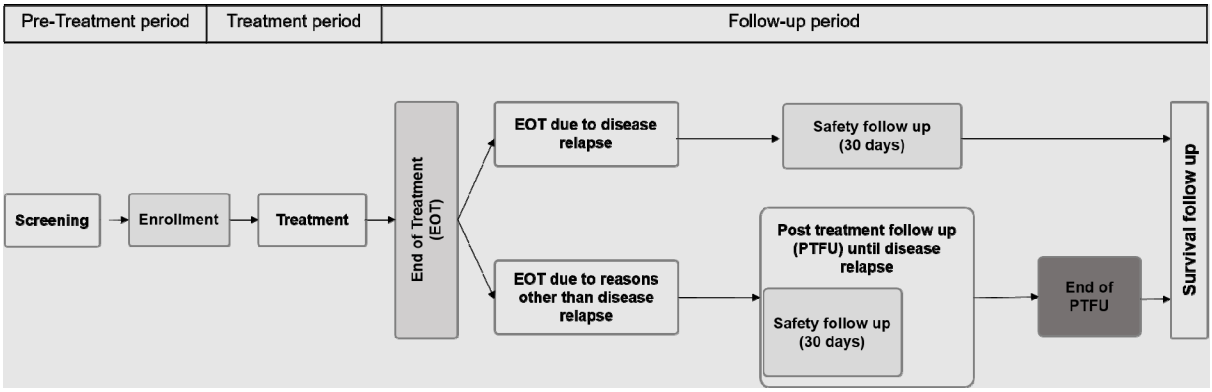
The study flow consists of 3 periods (see Figure 3-2): Pre-treatment (Screening), treatment and follow-up.

Participants will undergo assessments during screening and periodically during treatment and follow-up as outlined in Table 8-1 and Table 8-2.

An end of treatment (EOT) visit will be performed when participants permanently discontinue study treatment. Participants will then enter safety/post-treatment follow-up (PTFU) as shown in Figure 3-2 (also see Section 9.1.1.1 and Section 9.1.1.2).

All participants will be followed for survival as per Section 9.1.1.3.

Figure 3-2 Study Flow



4 Rationale

4.1 Rationale for study design

Rationale for the proposed treatment strategy

The curative effect of allo-SCT is dependent on the development of a robust GvL response of sufficient breadth and depth to eliminate all remaining malignant cells. However, the GvL response develops relatively slowly due to time necessary for engraftment and immune reconstitution post-transplant. In addition, mandatory, transient administration of IST required to suppress GvHD, also reduces the GvL effect.

Unfortunately, up to 40% of all relapses will occur within the first 6 months post-allo-SCT (Bejanyan et al 2015). Therefore, early treatments that support establishing GvL effects potentially through up-regulation of tumor antigens or acceleration of T cell reconstitution may be especially beneficial to post allo SCT patients (Loke et al 2020).

SORMAIN, a placebo-controlled study of FLT3-ITD-targeted therapy with sorafenib (N = 83) provided evidence that post-allo-SCT maintenance therapy can reduce the risk of relapse and death [HR for relapse or death in the sorafenib group vs placebo group was 0.39 (95% CI, 0.18 to 0.85; log-rank p = 0.013). Of note, 63% of the patients in the sorafenib group were either not in hematologic CR or not in molecular remission at time of allo-SCT, which was strongly predictive of poor survival. However, the relapse rate was only 15% after 2 years in the sorafenib arm, which appeared to be a clinically meaningful improvement (Burchert et al 2020).

With MDM2 inhibition, preclinical murine and human data showed upregulation of p53 expression in which is associated with upregulation in TP53 non-mutated leukemic cells of MHC-II and the pro-apoptotic receptors TRAIL-R1/2, which may reverse immune escape and enhance the anti-leukemia immunity post-allo-SCT (Nguyen Huong Giang Ho et al, in

preparation, confidential data on file). Therefore, these findings strongly support the use of siremadlin post-allo-SCT.

DLI is a treatment option with potential to enhance the GvL response and may contribute to improving outcomes and successfully prevent relapse after allo-SCT. However, DLI cannot be administered until 4-6 months post-allo-SCT due to the requirement to discontinue IST at least 4 weeks prior and to have any GvHD resolved. Therefore, preventing early disease relapse with the early use of siremadlin monotherapy priming can, in principle, allows a larger proportion of patients to receive subsequent siremadlin/DLI combination therapy.

Further, studies of DLI in AML have suggested that optimal use may require combination therapy that would further enhance the GvL effect, based on the assumption of synergistic antitumor effects without adding toxicity. Convincing data supporting the combination of DLI with a novel agent came from a retrospective study evaluating salvage therapy with the multikinase inhibitor sorafenib for post-transplant relapse of FLT3-ITD mutant AML. The subgroup of patients who received DLI in addition to sorafenib benefitted most and achieved a 3-year OS of 40%. Mechanistic analyses showed that sorafenib stimulated IL-15 production in the FLT3-ITD leukemic cells in responding patients, resulting in metabolic reprogramming and activation of leukemia-reactive CD8 donor αβ T cells (Mathew et al 2018).

The combination treatment of siremadlin plus DLI is strongly supported by preclinical data showing that MDM2 inhibition synergizes with the allogeneic immune response and increases the vulnerability of mouse and human AML cells to allogeneic T-cells (See further details in Section 4.3) (Nguyen Huong Giang Ho et al, in preparation, confidential data on file).

DLI are routinely administered over multiple cycles scheduled at 4 to 8 week intervals, guided by the occurrence of GvHD as limiting toxicity. Repetitive DLI might increase the chance to reverse T-cell exhaustion, hence justifying multiple DLI administrations in the setting of complete remission (Schmid et al 2021). In the prophylactic setting, due to increasing risk of GvHD with each DLI infusion, treatment is often limited to 3 or 4 cycles. However, AML may relapse up to 4 years post-allo-SCT, with the majority of relapses occurring during the first 2 years. These findings suggest that a treatment post-DLI might be necessary to ensure maintenance of the augmented GvL effect and subsequent suppression or clearance of residual leukemic cells for a prolonged period to prevent late-onset relapsing disease.

Taken together, a 3-part treatment strategy in study CHDM201K12201 in Part 2 is proposed, consisting of an early upfront priming with siremadlin monotherapy (at least 2 cycles), followed by a siremadlin combination with DLI (up to 3 cycles), followed by siremadlin maintenance monotherapy (for up to 24 cycles, all siremadlin treatment cycles included) in order to allow for an optimal and lasting treatment success in preventing early relapses and enhancing GvL post-allo-SCT in high-risk AML patients.

4.2 Rationale for dose/regimen and duration of treatment

Rationale for dose/regimen of siremadlin

The starting dose level for siremadlin for participants enrolled in this trial is set at 30 mg p.o. administered once daily on Days 1-5 of each cycle (one cycle = 28 days for siremadlin monotherapy, one cycle = 42 days for siremadlin/DLI combination). The selection of the

starting dose level and the treatment regimen for siremadlin monotherapy in the dose confirmation (Part 1) is based on currently available preclinical and clinical safety, efficacy, PK and PKPD modeling information from the single agent first-in-human clinical trial [CHDM201X2101].

In Study CHDM201K12201, the proposed mechanism of action is primarily dependent on immunomodulation and enhancement of the graft-versus-leukemia (GvL) effect. These immunomodulatory effects are hypothesized to occur at a lower dose of siremadlin as compared to the recommended dose for treatment of R/R (Relapsed Refractory) AML. Therefore, the proposed siremadlin dose levels in Study CHDM201K12201 (30 mg as a starting dose daily on days 1-5 of a 28-day cycle, dose level -1 at 20 mg daily, and dose level +1 at 40 mg daily) are lower, in terms of cumulative dose and maximum concentration, than the recommended dose for expansion established in patients with R/R AML in the first-in-human Study CHDM201X2101 (i.e., low-dose 2C at 45 mg daily on days 1-7).

The starting dose level of siremadlin of 30 mg in Part 1 is considered safe by a BLRM utilizing historical data from prior studies on siremadlin (refer to Section 16.6 for details).

In regards to the combination phase, siremadlin will be administered at 42-day interval between combination cycles (as opposed to 28-day interval between monotherapy cycles). The longer interval between DLIs is to evaluate for development of GvHD before the subsequent administration of DLI. Furthermore, the DLI starting dose, ramp up dosing and total number of DLI doses are strategies designed to minimize/prevent the risk of GvHD.

Study CHDM201X2101: Stein et al 2021 (ASH abstract) Subset analysis of 19 patients treated with siremadlin monotherapy for relapsed refractory AML after prior allo-SCT.

Among 91 patients with relapsed refractory (R/R) AML treated with siremadlin monotherapy in this first-in-human Study CHDM201X2101 (X2101) (NCT02143635), an exploratory post-hoc analysis of safety and preliminary efficacy was conducted on a subset of patients (n=19) who had undergone allo-SCT before study entry, and who have relapsed AML after allo-SCT and were subsequently treated with siremadlin monotherapy.

Eligible patients were ≥ 18 years with wild-type TP53 AML that have failed prior therapies. Siremadlin was administered to the 19 patients PO according to 4 different treatment regimens:

- 1A, 250 mg or 350 mg or 400 mg on day 1 of a 3-week cycle (n= 6)
- 1B, 120 mg or 150 mg on days 1 and 8 of a 4-week cycle (n= 4)
- 2A, 20 mg or 30 mg daily for the first 2 weeks of a 4-week cycle (n= 2)
- 2C, 45 mg daily for the first week of a 4-week cycle (n= 7)

Grading of adverse events was per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Response evaluation was per investigator's assessment based on the International Working Group for AML (Cheson et al 2003).

Demographics and baseline characteristics are summarized as follows: 19 patients with R/R AML after ≥1 allo-SCT had received siremadlin as salvage therapy for active disease [median leukemic blast at baseline from 18 out of 19 patients was 32% (range, 5%-94%)]. There were 10 (52.6%) male and 9 (47.4%) female patients. The median age was 64 years

(range: 30-72), 10 (52.6%) patients were <65 years and 9 (47.4%) patients were ≥65 years. The majority of patients was Caucasian (94.7%). Sixteen (84.2%) patients had an Eastern Cooperative Oncology Group (ECOG) performance status 0-1, and 3 (15.8%) patients had ECOG 2. Thirteen (68.4%) patients had received 1 prior allo-SCT, 5 (26.3%) had received 2 prior allo-SCTs, and 1 (5.3%) had received 3 prior allo-SCTs. The median interval from most recent allo-SCT to start of siremadlin was 308 days (range, 119-1105); with 3 (15.8%) patients within ≤180 days, 7 (36.8%) >180 to ≤ 365 days, and 9 (47.4%) >365 days post last allo-SCT. The median number of prior lines of antineoplastic therapy between most recent allo-SCT and study entry was 1 (range, 0-3), consisting of 4 (21%) patients who received no prior lines of therapy and 15 (79%) who received hypomethylating agent (azacitidine or decitabine) +/- chemotherapy and +/- donor lymphocyte infusion in 3 participants.

The median duration of exposure to siremadlin was 60 days (range, 21-203). The median dose intensity was 52.5 mg/day (range, 13.4-200) and the median cumulative dose was 630 mg (range, 250-1710).

In regards to safety, 16 (84.2%) and 14 (73.7%) patients experienced grade ≥3 AEs and treatment-related AEs, respectively; 14 (73.7%) and 12 (63.2%) patients experienced serious AEs (SAEs) and treatment-related SAEs, respectively. Nine patients had AEs leading to siremadlin dose adjustment or interruption, and 1 patient had an AE leading to treatment discontinuation (fungal sinusitis, grade 3, SAE, occurred on Study Day 155 and resolved on Study Day 189 (duration 35 days), was not suspected to be related to siremadlin). The most common grade 3/4 non-hematological AEs were febrile neutropenia (n=11, 57.9%), hypokalemia (n=5, 26.3%), and tumor lysis syndrome (n=3, 15.8%). Of these, n=5 (26.3%) febrile neutropenia, and n=3 (15.8%) tumor lysis syndrome were suspected to be related to treatment. The most common grade 3/4 hematological AEs were anemia (n=8, 57.9%), thrombocytopenia (n=7, 36.8%), neutropenia (n=6, 31.6%) and leukopenia (n=4, 21.1%). Of these, n=6 (31.6%) thrombocytopenia; n=6 (31.6%) neutropenia; n=5 (26.3%) anemia; and n=4 (21.1%) leukopenia, were suspected to be related to treatment.

Graft vs host disease (GvHD) was observed in 4 participants (21.1%): grade 3, n=2 (10.5%); grade 2 and grade 1, each n=1 (5.3%). The shortest time interval from most recent allo-SCT to study treatment in these 4 patients was 302 days (grade 3 GvHD was reported in this patient). Three of these 4 participants had a history of GvHD prior to commencement of siremadlin. Siremadlin was continued safely at full dose (n=3) or dose-reduced (n=1) in all four participants. For 1 participant treated with 400 mg in Reg 1A, chronic GvHD was declared a dose-limiting toxicity. Of note, some of these GvHD were reported as “suspected” or “possible” reactivation per the investigator's verbatim terms without confirmation of GvHD diagnosis.

Eleven patients were included in the dose determining set, and 3 (27.3%) patients had at least one event that was a dose limiting toxicity, including the aforementioned chronic GvHD. On-treatment deaths (occurring up to 30 days after end of treatment) were reported in 4 patients (2 AML-related, 1 euthanasia and 1 due to neutropenic infection). Overall, the safety profile was consistent with what was observed in the overall X2101 study population of hematologic malignancies (n=93) including n=91 R/R AML patients.

In regards to efficacy, among 19 evaluable patients, 3 achieved a clinical response: 2 achieved complete remission (CR) and 1 CR with incomplete hematologic recovery (CRi), lasting 171,

41, and 134 days, respectively. The overall response rate (CR or CRi or partial response) was 3/19 (15.8%) (95% confidence interval [3.4; 39.6]).

In conclusion, the safety of siremadlin monotherapy in patients with relapsed AML following prior allo-SCT(s) appears to be consistent with that previously defined in R/R AML (Stein et al 2022). No excessive GvHD was reported and siremadlin could be continued safely at full or reduced dose. Preliminary efficacy data indicate anti-leukemic activity of single-agent siremadlin. Despite the limitation of this post-hoc analysis, these results support further exploration of siremadlin immuno-modulatory effects post-allo-SCT as a potential maintenance or preemptive treatment in AML patients with high risk of relapse to enhance the allogeneic graft vs leukemia, an important and potent therapy against AML relapse.

Rationale for duration of study treatment

Although the optimal duration of maintenance therapy post-allo-SCT remains to be determined, it should theoretically ensure maintenance of augmented GvL (derived from the allo-grafted donor immune cells as well as from the administered DLI) and suppression of residual leukemic cell growth for a prolonged period during the time post-allo-SCT with the highest risk for relapse.

The proposed duration of 24 cycles (in total including siremadlin monotherapy and siremadlin/DLI combination) is supported by the reported time to relapse post-allo-SCT with the majority occurring within the first 2 years (in 1788 patients with AML who relapsed post-allo-SCT: median time to relapse was 7 months with 43% occurring within <6 months, 39% between 6 months-2 years, and 18% beyond 2 years post-allo-SCT) (Bejanyan et al 2015).

4.3 Rationale for choice of combination drugs (siremadlin with donor lymphocyte infusion)

While DLI has limited efficacy in treating relapsed AML post-allo-SCT, prophylactic DLI may contribute to improving outcomes in high risk AML and may successfully prevent relapse after allo-SCT. DLI has been found to increase anti-leukemic T cells, but also reverses T cell exhaustion through increased IFN-γ production and reduced T cell inhibitory receptors, such as programmed cell death protein 1 (PD-1) and T cell immunoglobulin and mucin domain 3 (Tim-3) (Sterling and Webster 2020, Liu et al 2018).

Further, prophylactic DLI recipients had a significantly improved 5-year OS [69.8% vs. 40.2% among controls; P = 0.027, HR = 0.387, 95% CI (0.116–0.898)] (Schmid et al 2019).

DLI is almost exclusively considered after discontinuation of immunosuppression for > 30 days and is not recommended with active GvHD and infections. GvHD is the main complication of DLI. The reported median interval from allo-SCT to first DLI was 4-6 months. In dose-escalating DLI administration protocols, 0.5-1 log increase and 4-6 week intervals are regarded as safe. Frequencies of DLI are typically guided by the occurrence of GvHD as limiting toxicity. In the prophylactic setting, and in the absence of GvHD, repeated DLI up to a total of 3 or 4 applications have been given. Repetitive DLI might increase the chance to reverse T-cell exhaustion, hence justifying multiple DLI administrations of DLI in the setting of complete remission of disease (Schmid et al 2021).

Based on published data/reports in prophylactic/maintenance setting post-allo-SCT, the low DLI starting dose [starting DLI dose ranging between 1 x 10^5 and 5 x 10^6 CD3+ T cells/kg depending on the donor type], ramp-up dosing, frequency and total number of DLIs [repeated infusions every 4-8 weeks with increase in CD3+ dose by 0.5-1 log at each infusion, up to a total of 3-4 applications] are strategies to minimize the risk of GvHD associated with DLI (Schmid et al 2021, Craddock et al 2021, Guillaume et al 2019, Caldemeyer et al 2017, Horn et al 2015).

For this study, the decision about DLI administration in eligible participants (Part 2) will be at the discretion of the treating investigator per the standard of practice/institutional guidelines.Based on the aforementioned rationale and published reports, the recommended starting DLI dose, for participants enrolled in this trial, is set at 2 × 10^5 CD3+ cells/kg for matched sibling/family donor (MFD), and at 1 × 10^5 CD3+ cells/kg 8/8 HLA-matched unrelated donor (MUD) to be administered on Day 3 of siremadlin. For subsequent DLI administrations, the CD3+ cell dose will be increased by 0.5 log increment with each infusion as compared to the prior DLI. The frequency of DLI infusion is recommended every 42 days, up to a total of 3 DLIs.

Rationale for combination of DLI with siremadlin

Refer to Background (Section 1.1) "Synergism of DLI in combination with pharmacologic approaches" for further details.

The combination of DLI with pharmacologic agents with immunomodulatory effects may enhance antitumor effects of DLI (GvL effect). Several phase I/II single-arm trials and retrospective studies have shown the feasibility of combining DLI and pharmacologic therapies, providing circumstantial evidence for DLI-based combinations (Schmid et al 2021).

Preclinical data from murine AML models showed that MDM2 inhibition synergized with the allogeneic immune response and increased the vulnerability of mouse and human AML cells to allogeneic T-cells. In leukemia-bearing mice treated with allo-SCT using bone marrow (BM) alone or in combination with T-cells, the addition of T-cells to the allogeneic BM graft improved survival. Treatment with MDM2-inhibitor in the absence of donor T-cells improved survival, but did not lead to long term protection. Only when T-cells were combined with MDM2-inhibition, > 80% of mice were protected long-term. The T-cell/MDM2-inhibitor combination did not increase acute GVHD severity compared to T-cells/vehicle. In addition, MDM2 inhibition promoted the cytotoxicity and longevity of the allogeneic donor CD8+ T cells as demonstrated by increased expression of the anti-tumor cytotoxicity markers (perforin, CD107a, IFN-γ, TNF and CD69), which resulted in long-term control of leukemia in murine models (Nguyen Huong Giang Ho et al, in preparation, confidential data on file).

In this study, the potential risks of siremadlin in combination with DLI, GvHD in particular, will be minimized by the stated criteria (see Section 6.1.4) that must be met before siremadlin/DLI combination therapy can be initiated. Among these criteria, tolerability of siremadlin, defined as the absence of any toxicity requiring siremadlin dose modification in the last cycle of priming therapy, is required. In the combination phase, siremadlin will be administered at the dose that was received and tolerated in the last cycle of priming phase (i.e., equivalent to the siremadlin starting dose level for priming or lower as per individual

adjustment) at 42-day interval between combination cycles (as opposed to 28-day interval between priming/monotherapy cycles). Hence, exposure to siremadlin is lower in the combination phase with DLI as compared to the priming phase due to the expanded cycle length.

The decision about DLI administration in eligible participants will be at the discretion of the treating investigator per the standard of practice. Recommendations for DLI starting dose, ramp up dosing and total number of DLI doses are specified in Section 6.3.1. For subsequent siremadlin/DLI cycle(s), absence of GvHD after the first siremadlin/ DLI combination cycle is required, as well as tolerability of siremadlin during the prior cycle (see Section 6.3.1 for details).

Taken together, the outlined dose and schedule for the siremadlin/DLI combination treatment as well as the defined criteria are appropriate measures for mitigation and minimization of the GvHD risk that is potentially associated with this combination treatment.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

The most common reported toxicities of siremadlin are hematological (neutropenia, thrombocytopenia, anemia) and gastrointestinal (nausea, vomiting, diarrhea).

Preclinical hERG study results suggest no potential clinical risk of QT prolongation; nevertheless, in context of limited clinical data, ECG monitoring is implemented in this study.

The risk to participants in this trial may be minimized by compliance with the eligibility criteria (e.g., well-defined thresholds of blood counts at study entry), and study procedures, as well as close clinical monitoring. Further, specific dose-limiting toxicity definitions, specific dose modification/interruption/discontinuation rules, prophylactic or supportive management of study-drug induced adverse events are included and must be applied as outlined in the protocol based on clinical and/or laboratory findings (Section 6.6).

Potential risk of GvHD exacerbation:

Immunomodulatory agents may represent effective maintenance or preemptive interventions aiming at enhancing GvL effect of the allogeneic graft, and potentially restoring/improving immune surveillance and destruction of malignant cells by allo-reactive donor T cells, hence preventing or delaying hematological relapse post-allo-SCT. However, enhancing GvL effect of the allogeneic graft may be associated with increased risk or worsening of GvHD, an immune-mediated toxicity and a major cause of non-relapse mortality after allo-SCT. Therefore, siremadlin-mediated enhancement of GvL could potentially exacerbate acute and/or chronic GvHD. In addition, GvHD is the main limiting toxicity associated with DLI with increasing risk with each DLI infusion.

Clinically significant acute and chronic GvHD following allo-SCT, contributing to post-allo-SCT morbidity and mortality, occur with reported incidence rates range from 9% to 50% for acute GvHD and from 30% to 70% for chronic GvHD (Flowers et al 2002,

Lee and Flowers 2008, Flowers et al 2011, Jagasia et al 2012, Flowers and Martin 2015, Vaughn et al 2015).

The incidence of GvHD varies based on several factors, including but not limited to degree of human leukocyte antigen (HLA) matching between the donor and recipient, graft source, conditioning regimen, and GvHD prophylaxis.

Although GvHD remains a serious and common complication of allo-SCT, a shift in maximal grade of acute GvHD and a decrease in the proportion of grade III-IV disease over time have been reported in a retrospective analysis of data from the CIBMTR registry on 2905 participants who developed grade II-IV acute GvHD following allo-SCT for hematological malignancies (56% AML) between 1999 and 2012 [grade III-IV GvHD 56%, 47%, and 37% for 1999-2001, 2002-2005, and 2006-2012, respectively]. The analysis also demonstrated a significant improvement in overall survival and treatment-related mortality overtime with a decline in deaths from organ failure and infection (Khoury et al 2017).

Notably, analysis of the impact of chronic GvHD and its severity indicates a close relationship between chronic GvHD and the immune-mediated GvL effect; as demonstrated with a lower risk of relapse translating into improved DFS with mild or moderate chronic GvHD compared to no chronic GvHD (Mo et al 2015).

As the safety of siremadlin has not been assessed previously in the post-allo-SCT setting, the protocol stipulates starting with 3-6 participants to obtain 3 evaluable participants for DLT assessment of siremadlin monotherapy with observation for at least one treatment cycle followed by a Safety Review Meeting, before opening enrollment to further participants. Further, participants will be evaluated for DLT during the siremadlin/DLI combination phase, as well as assessment of adverse events and further safety information during the maintenance phase with siremadlin monotherapy, as a part of standard safety monitoring.

Furthermore, the potential risks associated with siremadlin monotherapy and/or siremadlin/DLI combination, GvHD in particular, will be minimized by establishing criteria that must be met before start of priming phase, before combination therapy can be initiated, and before entering maintenance phase, as well as specifying the DLI starting dose, ramp up dosing, frequency and total number of DLI doses.

In addition, detailed guidance for study treatment modification (dose interruption, resumption and discontinuation) due to GvHD is included (Section 6.6).

Risk to the fetus:

Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

SARS-CoV-2 and COVID-19 pandemic:

No substantial additional risk for participants' safety due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus and the coronavirus disease 19 (COVID-19)

pandemic is anticipated and the benefit- risk remains unchanged. In case of active COVID-19 infection, a careful benefit-risk evaluation to be performed to determine whether participants can remain on study medication or not.

Unmet medical need:

Allo-SCT is a potentially curative treatment for AML, and the number of patients with AML eligible for allo-SCT has been increasing due to increased availability of donors (ie, haploidentical), development of less toxic (reduced intensity) conditioning regimens, and better management of GvHD, the principal toxicity associated with allo-SCT.

Unfortunately, up to 40% of patients with AML ultimately experience leukemic relapse, which is the main cause of treatment failure following transplantation (Thekkudan et al 2020) and the most common cause of death post-allo-SCT within the first 100 days (27%) and after day 100 (61%) (D'Souza et al 2020).

Furthermore, up to 40% of all relapses will occur within the first 6 months post-allo-SCT, likely due to a relatively slow development of a robust GvL response required to control the growth of residual leukemic cells. Such relapses are concentrated in a subpopulation of patients with high-risk features present pre-transplant. Thus, a treatment strategy that prevents early relapse post-allo-SCT in patients with high-risk features pre-transplant, and allows for the development of a robust GvL response would be a significant benefit for AML patients and represents a high unmet medical need.

ClinicalTrials.gov (as of 08-Jun-2020) lists more than 100 phase I-III interventional trials focusing on the prevention or treatment of relapse following allo-SCT, indicating that addressing this issue represents a major priority within the field (O'Neill and Chakraverty 2021).

Evidence of preliminary activity of siremadlin in AML, and the proposed mechanism of action including immunomodulation-mediated GvL enhancement, as well as the synergy with DLI-mediated anti-leukemia activity suggest that this treatment strategy (priming phase with siremadlin monotherapy, siremadlin/DLI combination, maintenance phase with siremadlin monotherapy) may be effective in prevention of AML relapse in the post-allo-SCT setting.

Although a potential risk associated with this treatment strategy, mild to moderate stimulation of GvHD may enhance GvL and translate into better overall outcome of patients.

Taking into consideration the risks associated with allo-SCT, the incremental risk of study treatment to the overall risk to patients in this trial is expected to be low.

In conclusion, the overall benefit/risk assessment is supportive of the conduct of this study in these AML patients at increased relapse risk post-allo-SCT based on the presence of high risk features pre-transplant, who represent a patient population with substantial unmet need with limited therapeutic options and dismal clinical outcomes.

4.6 Rationale for Public Health Emergency mitigation procedures

In the event of public health emergency as declared bylLocal or regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and

trial integrity are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional health authorities and ethics committees as appropriate.

[redacted]

5 Study Population

Study population includes adult patients with AML who underwent an allo-SCT and achieved remission but at high risk for relapse post-allo-SCT based on the presence of pretransplant risk factors as detailed in the inclusion criteria.

Approximately 38 participants are planned to be enrolled and treated.

The investigator or designee must ensure that only participants who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. At the time of signing the informed consent form (ICF), participants must be adults ≥ 18 years of age.
3. Participants with AML diagnosis, who underwent one allo-SCT to treat AML and are currently at ≥ Day 60 **but no later than Day 120 (≤ Day 120) post allo-SCT.**
4. **Pre-allo-SCT -** Participants must have any of the following risk factors that put them **at high risk for relapse**:
   - AML in first CR (CR1) prior to allo-SCT with one of the following:
     - Adverse risk genetic abnormalities per 2017 ELN risk stratification. Patients with TP53 mutant AML at diagnosis are eligible if they meet eligibility criteria.
     - Therapy-related AML (t-AML).
     - Secondary AML (sAML) [AML secondary to antecedent myelodysplastic syndrome (MDS) or AML secondary to myeloproliferative neoplasm (MPN)].
   - AML in second or greater CR (≥CR2) prior to allo-SCT.
5. **Allo-SCT** must have the following characteristics**:**
   - Unmanipulated/T cell-replete bone marrow or peripheral blood stem cells as a graft source.
   - Matched related (family) donor (MFD) or matched unrelated donor (MUD): Human Leukocyte Antigen (HLA) matching of donor and recipient should be at a minimum of 8/8 antigen or allele matched at HLA-A, -B, -C, -DRB1 loci.
   - Any conditioning regimen intensity is permitted, the use of anti-thymocyte globulin (ATG) or alemtuzumab or post-transplant cyclophosphamide as a part of conditioning is allowed.
6. Donor lymphocytes are collected, cryopreserved and available for infusion (DLI), or obtaining donor lymphocytes for DLI is feasible (applicable only for the Part 2).
7. **Post-allo-SCT,** participants must have achieved complete remission (CR) or CR with incomplete count recovery (CRi) with no current evidence of hematologic relapse (bone marrow blasts <5%; no circulating blasts in the blood; no evidence of extramedullary disease).
10. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.
11. Laboratory test results maximum 14 days prior to start of study treatment within the following ranges:
    - AST and ALT ≤ 3 × upper limit of normal (ULN).
    - Total bilirubin ≤ 1.5 × ULN (except in the setting of isolated Gilbert syndrome, in which case higher total bilirubin is allowed provided that conjugated bilirubin is ≤ 1.5 x ULN).

- Estimated Glomerular Filtration Rate (eGFR) ≥ 45 mL/min/1.73 m^2 (calculated, based on local laboratory, using the Modification of Diet in Renal Disease (MDRD) formula in adults).

12. Evidence of adequate engraftment post allo-SCT: ANC ≥ 1.0x10^9/L, platelet count ≥ 75x10^9/L, hemoglobin ≥ 8 g/dL (within 14 days prior to start of study treatment).

5.2 Exclusion criteria

Participants meeting **any** of the following criteria are not eligible for inclusion in this study.

1. Prior exposure to MDM-inhibitor.
2. Active acute GvHD of any grade (per Harris et al 2016) requiring systemic therapy at time of study treatment initiation.
3. Active chronic GvHD of any grade (per NIH criteria Jagasia et al 2015) requiring systemic therapy at time of study treatment initiation.
4. Past history of grade III or IV acute GvHD (per Harris et al 2016) and/or past history of moderate or severe chronic GvHD (per NIH criteria (Jagasia et al 2015)). History of lower grades of GvHD is permitted if GvHD resolved to grade 0 for at least 4 weeks prior to start of study treatment.
5. Recipient of allo-SCT from a matched unrelated donor (MUD) with one or more antigen or allele mismatch at HLA-A, -B, -C, -DRB1 locus (HLA matching less than 8/8 antigens).
6. Recipient of allo-SCT from a haploidentical family donor.
7. Recipients of cord blood transplant as a graft source.
8. Human immunodeficiency virus (HIV) infection not controlled by standard therapy and/or with known history of opportunistic infection.

   For countries where HIV status is mandatory: HIV status will be tested during screening using a local test.
9. Active Hepatitis B (HBV) or Hepatitis C (HCV) infection. Participants whose disease is controlled under antiviral therapy should not be excluded.
10. Prior systemic cancer-directed treatments or investigational modalities ≤ 5 half-lives or 4 weeks prior to starting study, whichever is longer.
11. Prior systemic AML-directed treatments given at any time after allo-SCT (including DLI).
12. History of another primary malignancy that is currently clinically significant or currently requires active intervention. Participants who are receiving adjuvant hormonal therapy for breast, prostate or other cancers are eligible.
13. Participants who require the use of herbal preparations/medications St. John's wort (*Hypericum perforatum*) within 7 days prior to first dose of study treatment or are expected to use such products during the entire study.
14. Participants who have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Starfruit within 3 days prior to the initiation of study treatment.
15. Participants who require treatment with moderate or strong CYP3A inducers within 14 days prior to starting study treatment, or are expected to receive moderate or strong CYP3A4 inducers during the entire study.

16. Use of live vaccines within 30 days prior to first dose of siremadlin.
17. Female participants who are pregnant or breastfeeding.
    - Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the study until 2 weeks after the last dose of siremadlin. Highly effective contraception methods include:
        - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
        - Female bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy at least six weeks before taking study treatment.
        - Male sterilization (at least 6 months prior to screening/baseline). For female participants on the study the vasectomized male partner should be the sole partner.
        - Use of an intrauterine device (IUD) or intrauterine system (IUS). The use of hormonal IUDs is allowed as their effect is local.

    Any form of systemic hormonal contraception for example oral, injectable, implanted, transdermal hormonal patch or hormonal vaginal ring are excluded from use. Hormonal systemic contraception is excluded as no appropriate clinical DDI studies have been conducted and there is a potential for siremadlin to reduce the effectiveness of hormonal contraceptive methods via CYP3A4 induction.
    - Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age-appropriate history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to enrollment on study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered to be not of child-bearing potential.
    - For male participants: A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner during the study until 2 weeks after the last dose of siremadlin. In addition, male participants should not donate sperm for the time period specified above.

    If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.
18. GI disorders that may prevent the intake and absorption of oral siremadlin (e.g., diarrhea, uncontrolled nausea and/or vomiting, GI bleeding, etc).
19. Any concurrent severe and/or active uncontrolled bacterial, viral or fungal infection requiring parenteral antibacterial, antiviral or antifungal therapy. Prophylactic antimicrobial use (oral or parenteral) is allowed.

20a. Cardiac or cardiac repolarization abnormality, including but not limited to any of the following:

- History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment.
- Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade Atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II and third degree AV block).
- QT interval corrected by Fridericia's formula (QTcF) interval > 470 ms.

Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA Grade III/IV).

21. Other concurrent severe and/or uncontrolled medical conditions or serious organ dysfunction or other co-morbidity that, in the opinion of the investigator, predisposes the participant to high risk of noncompliance with the protocol.

6 Treatment

6.1 Study treatment

In this study, the terms “investigational drug” and “study treatment” refer to the Novartis study drug, siremadlin.

All dosages prescribed, dispensed to the participant and all dose changes during the study including the reason for any treatment must be recorded on the appropriate electronic case report form (eCRF) page.

6.1.1 Investigational and control drugs

Table 6-1 Study Treatment

Study Drugs (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
Siremadlin (HDM201) 10 mg, 20 mg and 30 mg*	Capsule	Oral use (PO)	Open label, bottles	Global

*During the study,siremadlin (HDM201) 30 mg capsule may be included as additional strength which will be globally supplied

Refer to Section 6.3.2 for instruction for prescribing and taking study treatment

6.1.2 Treatment arms/group

In this Proof of Concept (PoC) study, the following treatments will be assessed:

Part 1: There will be one treatment arm that consists of siremadlin monotherapy. Refer to Section 6.3.1 for information on the regimen.

Part 2: There will be one treatment arm that consists of up to 3 consecutive phases: priming phase with siremadlin monotherapy; potentially followed by siremadlin/DLI combination phase; and then maintenance phase siremadlin monotherapy. Participants who will not be eligible for the combination phase will continue with siremadlin monotherapy only. Refer to Section 6.3.1 for information on the regimen.

6.1.3 Guidelines for continuation of treatment

Eligibility for combination phase of siremadlin with donor lymphocyte infusion (DLI):

The decision about DLI administration in eligible participants will be at the discretion of the treating investigator per the standard of practice/institutional guidelines. Participants who receive siremadlin in combination phase should be followed for safety and DLT evaluation as per Table 8-4.

Eligible participant must meet **all** of the following to start combination phase:

- **Immunosuppressive therapy (IST) taper has been completed for at least 4 weeks**.
- Continue to be in CR or CRi without evidence of hematologic relapse.
- No active aGvHD (per Harris et al 2016).
- No Grade III-IV aGvHD (per Harris et al 2016) during priming phase.
- No active cGvHD (per NIH criteria Jagasia et al 2015) during priming phase.
- Have received at least 2 cycles of siremadlin monotherapy (priming).
- Siremadlin has been tolerated (no siremadlin dose modification required for toxicity) during the cycle immediately preceding DLI.

In the absence of GvHD after first DLI dose, subsequent DLI can be administered.

Eligibility for siremadlin monotherapy in maintenance phase:

For participants who completed or discontinued of the combination phase with siremadlin/DLI, the following should be met for participants to proceed to **maintenance phase** with siremadlin monotherapy:

- Continue to be in CR or CRi without evidence of hematologic relapse.
- No active Grade II-IV aGvHD (per Harris et al 2016).
- No active moderate or severe cGvHD (per NIH criteria Jagasia et al 2015).
- For participants who developed GvHD during the combination phase requiring systemic GvHD treatment, starting maintenance phase with siremadlin monotherapy is permitted if GvHD has improved to ≤ Grade I for acute and/or to ≤ mild for chronic, with persistence of improvement for at least 2 weeks. Continuation of systemic GvHD treatment during maintenance phase is permitted and does not preclude initiation of siremadlin monotherapy (see Section 6.2.2.1 for drug-drug interactions).
- Adverse events / toxicities have resolved to ≤ CTCAE Grade 1 or to the participant's baseline value, per the investigator assessment.

In maintenance phase, siremadlin monotherapy will be administered starting at the dose that was tolerated in the last cycle of combination phase, orally on Days 1-5 of each 28-day treatment cycle. See Section 6.6.4 for further details of dose modifications.

6.1.4 Treatment duration

The planned duration of treatment is up to 24 cycles of siremadlin-containing cycles (including up to 3 cycles of siremadlin/DLI combination (Part 2) and for each cohort for the dose confirmation siremadlin monotherapy (Part 1). Participants may be discontinued from study treatment earlier due to:

- Disease relapse
- Unacceptable toxicity or intolerance
- Initiation of a new antineoplastic therapy (including allo-SCT).
- Other reasons as defined in Section 9.1.1 and Section 9.3.

For participants who discontinued study treatment due to development of GvHD following DLI and requiring systemic therapy, the treating investigator may consider resuming siremadlin as monotherapy without additional DLIs, considering the participant's benefit/risk balance of continuing siremadlin as per investigator's judgement (see Section 6.6.4 for details). In this case, the participants should continue to conduct the assessments outlined in Table 8-3 .

6.1.4.1 Treatment beyond disease progression

Treatment beyond disease progression is not permitted.

6.2 Other treatment(s)

6.2.1 Donor Lymphocyte Infusion (DLI)

DLI administration in eligible participants in Part 2 will be at the discretion of the treating investigator and it should be administered according to standard local clinical practice or institutional guidelines.

The starting dose, ramp-up dosing and frequency described must be followed as described in Section 6.3.1.2

All dosages prescribed, administered to the participant and all dose changes during the study including the reason for any treatment must be recorded on the appropriate electronic case report form (eCRF) page.

6.2.2 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered within 28 days of starting study treatment until 30 days after the last dose of siremadlin must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before enrolling a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.2.1 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution during study treatment in this study are listed below. For detailed guidance, please refer to appendix 4 (Section 16.4).

Systemic corticosteroids:

- For conditions other than GvHD or life-threatening emergencies, the use of systemic steroids and/or other immunosuppressive drugs should be limited and may only be administered for a limited duration, providing this is ≤ 10 mg/day prednisone or equivalent corticosteroid dose, in the following conditions:
  - For prophylaxis against imaging contrast dye allergy (higher doses for limited duration are permitted for local institutional practice).
  - For the management of transient exacerbation of other underlying diseases such as chronic obstructive pulmonary disease requiring treatment for ≤ 3 weeks.
  - For the management of infusion-related reactions (eg, Dimethyl sulfoxide (DMSO) with DLI infusion).
- Replacement dose corticosteroids in the setting of adrenal insufficiency are allowed.
- Non-systemic steroids (topical, inhaled, non-absorbable, nasal and ophthalmic steroids) are allowed.

Vaccines:

Inactivated vaccines, subunit, recombinant, polysaccharide and conjugate vaccines and toxoid vaccines are allowed.

Strong CYP3A inhibitors:

If such therapy is necessary, it can be introduced under the provision that the dose of siremadlin is reduced. Recommendation for the siremadlin dose, when given in combination with strong CYP3A inhibitors (e.g., posaconazole, ketoconazole, clarithromycin, indinavir, itraconazole, telaprevir, and voriconazole), are provided below:

1. Reduction level 1 is a dose reduction to **20%** of the planned dose per cycle (as provided in Table 6-2 below). The basis for this dose reduction is to mitigate potential safety concern given the 6-fold increase in siremadlin AUC observed with co-administration of itraconazole.
2. Reduction level 2 is a dose reduction to **30%** of the planned dose per cycle (as provided in Table 6-3 below). Application of dose reduction level 2 must not proceed until the investigators receive written confirmation from Novartis. The decision to adjust siremadlin dose reduction to level 2 may be taken upon review and evaluation of safety and siremadlin PK exposure data by the participating Investigators and Novartis study personnel. Safety data must be satisfactory and PK exposure not notably elevated and compatible with less significant dose reduction.

The basis of this siremadlin dose reduction is supported by physiologically based pharmacokinetic (PBPK) modeling in SimCyp and guided by the predicted fold-change of cumulative area under the curve (AUC) and Day 5 AUC.

Given that the lower dose strength of siremadlin capsules is 10 mg, approximations are made to round the reduced doses. The intermittent dosing in reduced doses of the 20 and 30 mg QD planned doses allows more time to clear the drug and thereby reduce the accumulation (applicable to both Table 6-2, Table 6-3 and Table 6-4).

Table 6-2 Management of potential interactions of strong CYP3A inhibitors with siremadlin - Reduction level 1 (to 20% of the planned dose)*

Dose Level of siremadlin	Dose without strong CYP3A inhibitor	Dose adjustment with strong CYP3A inhibitor
40 mg Total dose/cycle 200 mg	Day 1 – 40 mg Day 2 – 40 mg Day 3 – 40 mg Day 4 – 40 mg Day 5 – 40 mg	Day 1 – 10 mg Day 2 – 10 mg Day 3 – 0 (No dose) Day 4 – 10 mg Day 5 – 10 mg
30 mg Total dose/cycle 150 mg	Day 1 – 30 mg Day 2 – 30 mg Day 3 – 30 mg Day 4 – 30 mg Day 5 – 30 mg	Day 1 – 10 mg Day 2 – 0 (No dose) Day 3 – 10 mg Day 4 – 0 (No dose) Day 5 – 10 mg
20 mg Total dose/cycle 100 mg	Day 1 – 20 mg Day 2 – 20 mg Day 3 – 20 mg Day 4 – 20 mg Day 5 – 20 mg	Day 1 – 10 mg Day 2 – 0 (No dose) Day 3 – 0 (No dose) Day 4 – 0 (No dose) Day 5 – 10 mg
* Application of dose reduction level 2 must not proceed until the investigators receive written confirmation from Novartis		

Table 6-3 Management of potential interactions of strong CYP3A inhibitors with siremadlin - Reduction level 2 (to 30% of the planned dose)*

Dose Level of siremadlin	Dose without strong CYP3A inhibitor	Dose adjustment with strong CYP3A inhibitor
40 mg Total dose/cycle 200 mg	Day 1 – 40 mg Day 2 – 40 mg Day 3 – 40 mg Day 4 – 40 mg Day 5 – 40 mg	Day 1 –10 mg Day 2 – 10 mg Day 3 – 10 mg Day 4 – 10 mg Day 5 – 20 mg
30 mg Total dose/cycle 150 mg	Day 1 – 30 mg Day 2 – 30 mg Day 3 – 30 mg Day 4 – 30 mg Day 5 – 30 mg	Day 1 – 10 mg Day 2 – 10 mg Day 3 – 10 mg Day 4 – 10 mg Day 5 – 10 mg
20 mg Total dose/cycle 100 mg	Day 1 – 20 mg Day 2 – 20 mg Day 3 – 20 mg Day 4 – 20 mg Day 5 – 20 mg	Day 1 – 10 mg Day 2 – 0 (No dose) Day 3 – 10 mg Day 4 – 0 (No dose) Day 5 – 10 mg
* Application of dose reduction level 2 must not proceed until the investigators receive written confirmation from Novartis		

Moderate CYP3A inhibitors:

If such therapy is necessary, it can be introduced under the provision that the dose of siremadlin is reduced. Recommendation for siremadlin dose, when given in combination with moderate CYP3A inhibitors (such as erythromycin, fluconazole, ciprofloxacin, isavuconazole), are provided in Table 6-4 below.

The basis adjustment of the siremadlin dose to **40%** of the planned dose per cycle in case of concomitant administration of moderate CYP3A inhibitor is supported by physiologically based pharmacokinetic (PBPK) modeling in SimCyp and guided by the predicted fold-change of cumulative AUC and Day 5 AUC.

Table 6-4 Management of potential interactions of moderate CYP3A inhibitors with siremadlin

Dose Level of siremadlin	Dose without moderate CYP3A inhibitor	Dose adjustment with moderate CYP3A inhibitor
40 mg Total dose/cycle 200 mg	Day 1 – 40 mg Day 2 – 40 mg Day 3 – 40 mg Day 4 – 40 mg Day 5 – 40 mg	Day 1 – 10 mg Day 2 – 10 mg Day 3 – 20 mg Day 4 – 20 mg Day 5 – 20 mg
30 mg Total dose/cycle 150 mg	Day 1 – 30 mg Day 2 – 30 mg Day 3 – 30 mg Day 4 – 30 mg Day 5 – 30 mg	Day 1 – 10 mg Day 2 – 10 mg Day 3 – 10 mg Day 4 – 10 mg Day 5 – 20 mg
20 mg Total dose/cycle 100 mg	Day 1 – 20 mg Day 2 – 20 mg Day 3 – 20 mg Day 4 – 20 mg Day 5 – 20 mg	Day 1 – 10 mg Day 2 – 10 mg Day 3 – 0 (No dose) Day 4 – 10 mg Day 5 – 10 mg

Antifungal therapy with azole agents is an important standard of care in AML patients. However, all azole antifungal agents carry drug-drug interaction liabilities because of their moderate to strong inhibitory effects on cytochrome CYP3A enzyme. Siremadlin, as a substrate for CYP3A, has a potential for increased exposure in participants concomitantly treated with azole agents, which might have an impact on safety and tolerability.

Indeed, in a drug interaction study in healthy volunteers ([CHDM201X1102]) that investigated the effect of itraconazole (strong CYP3A inhibitor) on the pharmacokinetic properties of siremadlin, itraconazole administered with a single dose of siremadlin increased mean Cmax and AUCinf of siremadlin by 1.42- and 6.13-fold, respectively, compared with siremadlin alone. Since siremadlin will be used in a patient population that frequently requires concomitant medications with azole antifungals (eg, especially posaconazole) or antibiotics, guidelines on dose adjustment of siremadlin would be required when co-administered with strong or moderate CYP3A inhibitors. Information gained from this trial would allow for the confirmation of the proposed dose adjustment in the patient population or alternatively may be used to inform on instructions for different or refined dose adjustment requirements. This will be based on the comparison of PK systemic exposure of siremadlin in participants not requiring and then requiring concomitant administration of strong or moderate CYP3A inhibitors and conversely if possible (depending upon the observed data), and also from the PK exposure data with and

without strong and moderate CYP3A inhibitors of this trial (and other trial(s) with similar approach if applicable). This will be further supported by PBPK modeling based on the available data.

Anti-GvHD medications with narrow therapeutic index substrates of CYP3A (e.g. tacrolimus, cyclosporine, sirolimus)

If systemic GvHD prophylaxis or treatment [immunosuppressive therapy (IST)] taper has not been started or completed at study entry, IST taper schedule and duration will be per institutional guidelines and at the discretion of the treating investigator.

Tacrolimus, cyclosporine, sirolimus are IST agents and are all sensitive CYP3A substrates.

In vitro siremadlin was identified as a reversible and time-dependent inhibitor and as an inducer of CYP3A. Drug-drug interactions (DDI) of siremadlin with IST agents cannot be predicted based on in vitro data.

Therefore increased systemic exposure of tacrolimus, cyclosporine, or sirolimus in presence of siremadlin cannot be excluded.

Owing to the narrow therapeutic index of these IST agents, drug levels of cyclosporine, tacrolimus, and/or sirolimus will be measured by local laboratories before (within approximately a week) and during siremadlin administration, monitored and reported (see Table 6-5).

The desired IST target range during IST taper will be per the local institutional standard of practice and at the discretion of the treating investigator.

For IST blood levels measured before siremadlin administration (approximately a week):

- If IST blood levels are within the desired range, no IST dose change reduction is needed.
- If IST blood levels are notably higher or lower, the IST dose will be adapted as needed as per the local institutional standard of practice and at the discretion of the treating investigator.

Table 6-5 Timepoints for IST drug level measurements to be recorded by investigators

Time relative to siremadlin administration (D1-5) of a given cycle	Cyclosporine Trough[2] ng/mL	Cyclosporine 2-hour concentration (C2)[2] ng/mL	Tacrolimus Trough ng/mL	Sirolimus Trough ng/mL	Action taken by investigator for IST dose adjustment (if applicable)	Selected Clinical measures [3]
Within approximately 1 week before[1]						
D1 of siremadlin						
D5 of siremadlin						

(1) Report the last IST level measurements within the week before starting siremadlin. If not possible, IST levels from up to 8-9 days before are acceptable

Time relative to siremadlin administration (D1-5) of a given cycle	Cyclosporine Trough[2] ng/mL	Cyclosporine 2-hour concentration (C2)[2] ng/mL	Tacrolimus Trough ng/mL	Sirolimus Trough ng/mL	Action taken by investigator for IST dose adjustment (if applicable)	Selected Clinical measures [3]

(2) Either cyclosporine trough level or cyclosporine 2-hour concentration (C2) level can be measured per the local institutional standard of practice.
(3) Selected clinical measures include signs and symptoms not already recorded under safety assessments that indicate high or low IST levels, such as GvHD exacerbation, nephrotoxicity, hepatotoxicity, and other toxicities.

Participants who are receiving azole antifungals (strong or moderate inhibitors of CYP3A) simultaneously with siremadlin and IST agent(s) (cyclosporine, tacrolimus, and/or sirolimus), the recommendation for siremadlin dose adjustment when combined with azoles must be followed as outlined inTable 6-2, Table 6-3 and Table 6-4 for strong and moderate inhibitors of CYP3A, respectively. Monitoring will be followed as per the local institutional standard of practice and local labels.

For additional information on the PK properties and interaction, please refer to local labels of tacrolimus, cyclosporine, sirolimus, and to [Siremadlin (HDM201) Investigator's Brochure].

Additional therapeutic monitoring references are made to (Clinical Guidelines for Transplant Medications. BC Transplant. 2019 and McCune and Bemer 2016).

Some PK properties and therapeutic monitoring indications are summarized below:

- **Cyclosporine** is an inhibitor of CYP3A4 and the multidrug efflux transporter P-glycoprotein. Cyclosporine is extensively metabolised to approximately 15 metabolites. Metabolism mainly takes place in the liver via cytochrome P450 3A4 (CYP3A4). Mutual interaction of cyclosporine and siremadlin cannot be excluded. There is a high variability in the data reported on the terminal half-life (T1/2) of ciclosporin depending on the assay applied and on the target population. T1/2 ranged from 6.3 hours in healthy volunteers to 20.4 hours in patients with severe liver disease. T1/2 in kidney-transplanted patients was approximately 11 hours, with a range between 4 and 25 hours. Evidence shows that the monitoring of cyclosporine at the 2 hour concentration point (C2) is the most accurate single time point for assessment of cyclosporine absorption and immunosuppressive effect. By monitoring C2 target concentrations in renal and liver transplant recipients one can more accurately adjust the patients' cyclosporine dose to minimize toxicity and rejection rates. However, C2 measurements are not done in all patients and some stem cell transplant institutions use cyclosporine trough concentration for drug level monitoring (Clinical Guidelines for Transplant Medications. BC Transplant. 2019, McCune and Bemer 2016).
- **Sirolimus** is extensively metabolised by the CYP3A4 isozyme in the intestinal wall and liver. Sirolimus is also a substrate for the multidrug efflux pump, P-glycoprotein (P-gp) located in the small intestine. Therefore, absorption and the subsequent elimination of sirolimus may be influenced by substances that affect these proteins. Following the administration of sirolimus oral solution, sirolimus is rapidly absorbed, with a time to peak concentration of 1 hour in healthy volunteers receiving single doses and 2 hours in patients with stable renal allografts receiving multiple doses. The terminal half-life in stable renal transplant patients after multiple oral doses was 62 ±16h. The effective half-life, however,

is shorter and mean steady-state concentrations were achieved after 5 to 7 days. Whole blood trough levels of sirolimus should be closely monitored in the following populations when inducers or inhibitors of CYP3A4 are concurrently administered and after their discontinuation.

- Systemically available **tacrolimus** is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. Tacrolimus is a known (weak) CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolised by CYP3A4 may affect the metabolism of such medicinal products. The half-life of tacrolimus is long and variable. In healthy volunteers, the mean half-life in whole blood is approximately 43 hours. Further, (McCune and Bemer 2016) reported that tacrolimus has a volume of distribution of 1.67 L/kg, oral bioavailability of 31–49% and a half-life of 18.2 hours. A strong correlation exists between AUC and whole blood trough levels at steady-state for tacrolimus. Therefore, monitoring of whole blood **trough levels of tacrolimus** provides a good estimate of systemic exposure. As tacrolimus is a substance with low clearance, adjustments to the tacrolimus dose regimen may take several days before steady state is achieved.

There is a low potential of interaction related to impact of IST agents on siremadlin, which will be investigated by PK concentration collected for siremadlin.

6.2.2.2 Use of bisphosphonates

Bisphosphonates may be given according to their local product license and routine clinical practice, at the investigator's discretion.

No drug-drug interaction is expected between siremadlin and bisphosphonates. Bisphosphonates are not inhibitors of human CYP450 enzymes and do not undergo metabolism in vivo.

6.2.3 Prohibited medications

- During course of the study, no additional investigational drugs, devices, chemotherapy, immunotherapy or any other therapies that may be active against cancer or modulate the immune response would be allowed. DLI will not be permitted on study during Part 1.
- The use of live vaccines is not allowed through the duration of the study treatment and at least 30 days after the last dose of siremadlin or longer as applicable per vaccination guidelines post-allo-SCT.
- Prior to starting DLI in combination with siremadlin, IST taper must have been completed for at least 4 weeks. The use of systemic corticosteroids and/or immunosuppressive treatment is not allowed during DLI cycles in combination with siremadlin unless given for the conditions listed in the concomitant medications in Section 6.2.2.1
- Strong or moderate CYP3A inducers: Concomitant use of strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) are prohibited within 14 days prior to start and

during the study treatment period as siremadlin is primarily metabolized by CYP3A4. Alternative treatments with less CYP3A induction should be considered.

- Use of the herbal preparations/medications with St. John's wort are prohibited during study treatment period due to potential drug-drug interaction. Participants should stop using these herbal medications 7 days prior to first dose of study drug.
- Use of CYP3A substrates with a narrow therapeutic index (NTI) are prohibited 24 hours before and 48 hours after siremadlin administration as in vitro experiments have shown siremadlin to be both a time-dependent and reversible inhibitor of CYP3A4/5. For anti-GvHD medications with narrow therapeutic index substrates of CYP3A see under Section 6.2.1.

Refer to Table 16-4 in appendix 4 (Section 16.4) for a detailed list of prohibited concomitant medications.

6.2.4 Supportive care measures

Participants should receive appropriate supportive care measures (including blood product support, anti-emetics, anti-diarrheal treatment, prophylactic or therapeutic anti-microbials, pre-medication prior to DLI administration, etc.) at the discretion of the treating Investigator and per the local standard of practice (refer to Section 6.3.2). However, each additional medication must be individually assessed against all exclusion criteria/prohibited medications and for potential drug-drug interactions (refer to concomitant/prohibited medications, appendix 4 Section 16.4).

6.3 Preparation and dispensation

Each study site will be supplied with siremadlin in packaging as described under investigational and control drugs section (Section 6.1.1).

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

DLI may be administered as fresh product or cryopreserved product after thawing. Procedures for DLI processing, cryopreservation, thawing and administration will be according to the local institutional practice. For further details please refer to Section 6.3.1.2

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of siremadlin directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of siremadlin from the site to the participant's home remains under the accountability of the Investigator.

Each shipment/provisioning will be for a maximum of 2-months supply. In this case, regular phone calls or virtual contacts (every 4-weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

For study drugs administered at home, participants will be asked to return all unused study drugs and packaging to the site at the next visit and at the end of the study or at the time of discontinuation of study treatment. The investigator may provide a drug diary with detailed instructions to the participant to facilitate treatment compliance.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.3.1.2 Handling of other treatment

Donor Lymphocyte Infusion (DLI): For eligibility requirements that must be met before starting siremadlin/DLI combination phase, please refer to Section 6.1.3.

DLI is a cellular therapy, which is used in the population enrolled in this study. The decision about DLI administration in eligible participants will be at the discretion of the treating investigator and it should be administered according to standard local clinical practice or institutional guidelines. However, the starting dose, ramp-up dosing and frequency described below must be followed.

Pre-medication prior to DLI administration: Per local standard of practice. However, participants should not receive systemic corticosteroids prophylactically as a pre-medication to

prevent infusion-related reaction (ie, to DMSO) unless a participant experienced a prior clinically significant infusion-related reaction (eg, anaphylactic/anaphylactoid reactions).

Immunosuppressive therapy (IST)/GvHD prophylaxis/treatment: Participants who have not completed IST taper prior to start of study treatment will continue to receive IST and tapering according to local standard of practice and as clinically appropriate. However, instructions for level monitoring and dose adjustments pre-, during, and post-siremadlin administration must be followed as in Section 6.2.2.1 and Table 6-5 for anti-GvHD medications with narrow therapeutic index substrates of CYP3A.

Starting DLI dose: DLI should be administered, after siremadlin, on day 3 of a 42-day (6-week) combination cycle, starting at a low dose based on donor type as follows:

- Matched sibling/family donor (MFD): 2×10^5 CD3+ cells/kg
- 8/8 HLA-matched unrelated donor (MUD): 1×10^5 CD3+ cells/kg

Subsequent DLI administration:

- In the absence of GvHD exacerbation after first DLI dose, DLI can be repeated (DLI ramp-up dosing) with the next combination cycle within 42 days in combination with siremadlin.
  - DLI should be administered, after siremadlin, on day 3 of a 42-day (6-week) combination cycle.
  - DLI ramp-up dosing: increase CD3+ cell dose by 0.5 log increment with each subsequent infusion as compared to the prior DLI dose, for up to a total of 3 DLIs.
- In the absence of clinically significant GvHD and the absence of hematologic overt relapse, continue with DLI in combination with siremadlin for up to a total of 3 cycles with DLI/siremadlin combination.

In case of development of or exacerbation of GvHD of any severity following DLI administration, please refer to Section 6.6.4.

6.3.2 Instruction for prescribing and taking study treatment

Table 6-6 Dose and treatment schedule

Study Drugs	Dose	Frequency	Regimen
Siremadlin	As assigned Starting dose level: 30 mg	**Daily on days 1 to 5** of every cycle: ● 28-day cycle during Part 1, priming and maintenance phases (monotherapy) ● 42-day (6-week) cycle during combination phase with DLI (siremadlin/DLI combination)	QD fasted

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

Siremadlin

Participants should take siremadlin on an empty stomach (i.e. fast from food and drink, except water) at least 1 hour before or 2 hours after a meal. The participant should take the capsules in the morning, at approximately the same time each day of dosing, with a glass of water and without chewing the capsules.

If the participant is assigned to a dose level where multiple capsules are to be taken, the capsules should be taken consecutively, within as short an interval as possible. On the visit days, the participant will take siremadlin at the clinic under the supervision of the investigator or designee and on other days at home.

If a participant misses doses of siremadlin within 8 hours of the time it is usually taken, the participant should take the missed dose as soon as possible on the same day. If the participant misses a dose by more than 8 hours, the participant should not take the missed dose and should resume the usual dosing schedule at the usual time the following day. Any missed dose should be reported to the Investigator at the next study visit. If a participant vomits after taking siremadlin, the dose should not be re-administered and the participant should take their next dose at the usual time the following day.

On days that PK samples are obtained, the participant will be instructed to bring his/her siremadlin capsules to the clinic and take siremadlin during the clinic visit after the pre-dose PK sampling and prior to post-dose PK sampling, under the supervision and when instructed by the study staff. The exact time for dose administration and breakfast intake must be recorded in the source documents and eCRF. In addition, on the days of full PK sampling, if a participant vomits within the first 4 hours after dose administration, the exact time of the first episode of vomiting should be recorded on the CRF and the dose should not be re-administered.

A reduced dose of siremadlin per day with concomitant use with either strong or moderate CYP3A inhibitors is necessary (see Section 6.2.2.1).

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained as a primary identifier for the participant throughout his/her participation in the trial.

The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database.

Upon signing the informed consent form, the site will use the electronic data capture system (eCRF) to assign the participant to the next sequential Participant No. available.

The investigator or designated staff will then contact the Interactive Response Technology (IRT) and provide the requested identifying information (including the assigned Participant No.) to enroll the participant. Once assigned, the participant No. must not be reused for any other participant and the participant No. for that individual must not be changed, unless the participant is re-screened.

If the participant fails to start treatment for any reason, the reason will be entered into the appropriate eCRF page and IRT should be notified as soon as possible. Re-screening is allowed once for participants that were initially screen failures for any reason. A new ICF will need to be signed and all eligibility criteria must be re-checked and met prior to enrollment of the

participant into the study. A new participant No. should be assigned for all re-screened participants.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.4.2 Treatment assignment, randomization

No randomization will be performed in the study.

The assignment of a participant to a particular dose cohort will be using the IRT system and will be coordinated by Novartis.

Following screening and prior to dosing at C1D1, the investigator (or delegate) will call or log on to the IRT and confirm that the participant fulfills all the inclusion/exclusion criteria by completing the eligibility criteria checklist embedded in the system. The IRT will assign a unique medication number for the investigational drug: siremadlin.

6.4.2.1 Replacement policy

Dose confirmation part

Participants will not be replaced on study. However, if a participant is considered as non-evaluable for the escalation decisions, enrollment of a new participant to the current cohort will be considered if there is less than the required number of evaluable participants. Enrollment of new participants may be considered until at least the minimum number of evaluable participants is achieved within the cohort (refer to Section 12.8.1). Minimum and maximum numbers of evaluable participants per cohort are defined in the guidelines for dose escalation and determination section.

6.5 Treatment blinding

Not applicable.

6.6 Dose escalation and dose modification

Up to three dose levels of siremadlin may be evaluated during Part 1, if applicable. The assessment of the tested dose levels of siremadlin as monotherapy will be guided by a BLRM with overdose control criteria (EWOC) based on the DLT incidence reported during the first cycle as well as an overall safety overview for participants included in the DDS1. Based on the safety assessment, the decision on the siremadlin RD for priming in subsequent cohort will be made.

For the combination phase, the assessment of participants' siremadlin dose levels for combination phase will be guided by a Bayesian time-to-DLT model with overdose control criteria (EWOC) based on the DLT incidence reported in each cycle of combination phase for participants in DDS2. The siremadlin recommended dose for combination will be determined based on the safety assessment.

Intra-participant dose escalation is not permitted for any of the treatment phases. Guidance for dose modifications is provided in Section 6.6.4.

6.6.1 Dose escalation guidelines

6.6.1.1 Starting dose

The starting dose level of siremadlin monotherapy in Part 1 is 30 mg p.o. administered once daily on Days 1-5 of each cycle [one cycle = 28 days] (see Section 4.2 for dose selection rationale).

6.6.1.2 Provisional dose levels

Table 6-7 describes the starting dose level in Part 1 and the dose levels that may be evaluated during this part. Refer to Section 4.2 for siremadlin dosing rationale.

Table 6-7 Provisional siremadlin dose levels

Dose level	Proposed daily dose	Increment from previous dose
-1**	20 mg	-33%
1	30 mg	Starting dose
+1	40 mg	+33%

**Dose level -1 represents treatment dose for participants requiring a dose reduction from the starting dose level. No dose reduction below dose level -1 (20 mg) is permitted for this study.

6.6.2 Guidelines for dose escalation, determination of recommended dose for part 1 and maximum recommended dose for combination in part 2

Dose confirmation siremadlin monotherapy phase (Part 1)

For the purposes of assessing the risk of overdosing (as defined by EWOC criterion, see details below) of siremadlin monotherapy, participants must be in the dose-determining set of the Part 1 (DDS1) (details in Section 12.1).

If one or more participants fail to meet the evaluability criteria, the replacement policy (see Section 6.4.1) may be used to enroll additional participants to the same cohort, in order to support the benefit-risk assessment.

Dose de-escalation decisions will occur after the required number of evaluable participants have completed Cycle 1. The first cohort of at least 3 evaluable participants will be treated at the starting dose level of siremadlin (DL1) 30 mg QD Days 1-5 of a 28-day cycle.

If the EWOC criterion is satisfied (probability of excessive toxicity is lower than 25%), the Bayesian model will recommend to open a second cohort of at least 6 evaluable participants at the next dose level (DL+1) at 40 mg. If the decision is to de-escalate to 20 mg (DL-1), a second cohort will enroll at least 6 evaluable participants. If the decision is to maintain 30 mg, a second cohort will enroll at least 3 evaluable participants.

A dose level to be declared as RD must be tested with at least 6 evaluable participants. The siremadlin RD for priming will be selected among 20 mg, 30 mg and 40 mg, considering additional safety information beyond the first cycle (DLT observation period) and available clinical pharmacology data, tolerability data, and recommendations from participating investigators.

To reduce the risk of exposing participants to an overly toxic dose in Part 1, when 2 participants experience a DLT in a new cohort, the BLRM will be updated with the most up-to-date new information from all cohorts, without waiting for all participants from the current cohort to complete the evaluation period. If the two DLTs occur in a de-escalation cohort, enrollment to that cohort will stop.

Dose de-escalation decisions will be made by participating Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade ≥ 2 toxicity data during DLT observation period, if possible PK, and PD (optional) data from evaluable participants. The recommended dose for the next cohort of participants will be guided by the statistical models with EWOC principle.

Once the recommended siremadlin dose is determined in Part 1, enrollment in Part 2 will start after having obtained Health Authority's approval as applicable. Enrollment in Part 2 will not be applicable to participating sites in the United States and Germany.

Combination phase (in Part 2)

DLT evaluation will be performed for all participants over the entire siremadlin/DLI combination phase. Safety assessments will be conducted after each cohort of 3 participants completed the first siremadlin/DLI treatment cycle or experienced a DLT event. After the first assessment, a maximum dose for siremadlin will be provided by a Bayesian time-to-(first) DLT model and used as an upper limit for participants to enter combination phase The maximum dose will be updated continuously following safety assessments taking into consideration all available information, also from cycles after Cycle 1. The final safety assessment will take place after all participants in dose-determining set 2 (DDS2) (see DDS2 of the combination phase in Section 12.1) complete combination phase. Determination of the siremadlin maximum RD for combination requires a minimum of 9 evaluable participants and satisfies EWOC principle for each of the three cycles of combination phase. A dose level to be declared as maximum RD for combination must be tested with at least 3 evaluable participants treated at or above that dose level.

6.6.2.1 Implementation of dose escalation decisions

To implement dose escalation decisions for Part 1, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the recommendations from the BLRM, if possible available PK and PD (optional) information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Similarly, decisions to reduce participants' dose levels for the combination phase (Part 2) will be made on basis of all available toxicity information, the recommendations of the time-to-DLT model, and other relevant information by the Investigators and Novartis study personnel.

Drug administration at the next larger dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a larger dose level.

6.6.2.2 Intra-Participant dose escalation

Intra-participant dose escalation is not permitted.

6.6.3 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed, by the Investigator, to be at least possibly related to study treatment (siremadlin monotherapy and/or siremadlin in combination with DLI), and as unrelated to disease, disease progression, inter-current illness, or concomitant medications, that occurs during the DLT observation period and meets any of the criteria included in Table 6-8. These DLT criteria apply for both Part 1 and Part 2.

The DLT observation period will be within the first treatment cycle with siremadlin monotherapy in Part 1, and within the complete Part 2 (starting at day of first DLI and ending at end of the last siremadlin/DLI cycle).

A participant meets the minimum dose criteria if he/she received during the first cycle at least 75% of the total planned doses for siremadlin (e.g., ≥ 4 out of 5 daily doses of siremadlin (Part 1 and Part 2).

Participant meets the minimum dose criteria if he/she received the planned dose of DLI and at least 75% of the total planned doses for siremadlin as defined in the dose and treatment schedule (see Section 6.3.2) for a given cycle (Part 2).

The National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 5.0 will be used for all grading except for GvHD; (Harris et al 2016) will be used for acute GvHD, and NIH consensus criteria will be used for chronic GvHD (Jagasia et al 2015).

For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM (Part 1).

The investigator must notify the sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities that are not consistent with the observed safety profile of siremadlin or any adverse events meeting DLT criteria. Prior to enrolling participants into a larger dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all participants at the current dose level.

If a participant experiences a DLT (during the DLT observation period) then study treatment must be interrupted and may be permanently discontinued depending on the severity of and recovery from the DLT (refer to Table 6-9 and Section 6.6.4). If the DLT (other than GvHD) resolves to CTCAE grade 1 or baseline value, the participant may continue to receive study treatment following consultation with the Novartis medical monitor.

For acute GvHD and/or chronic GvHD that meet DLT criteria, refer to Section 6.6.4 for study treatment interruption, re-initiation and/or discontinuation.

Table 6-8 Criteria for defining dose limiting toxicities

Toxicity	DLT criteria
DLTs considered related to graft vs host disease (GvHD) by the Investigator assessment	
GvHD	Grade 3 - 4 acute GvHD [per Harris et al 2016
	Moderate chronic GvHD [per NIH criteria]
	Severe chronic GvHD [per NIH criteria]
Other DLTs excluding acute or chronic GvHD by the investigator assessment	
Hematology (in the absence of leukemic infiltration in the bone marrow)	Grade 4 neutropenia and/or thrombocytopenia, that do not respond to growth factor or transfusion support within 14 days
	Grade ≥ 3 febrile neutropenia
	Grade ≥ 3 thrombocytopenia with clinically significant bleeding
GI (not considered related to GvHD)	Grade 3 nausea and vomiting, that do not resolve to ≤ Grade 1 within 48 hours of starting anti-emetic therapy
	Grade 4 nausea and vomiting (regardless of duration)
	Grade 3 diarrhea, that do not resolve to ≤ Grade 1 within 48 hours of starting anti-diarrhea treatment
	Grade 4 diarrhea (regardless of duration)
Liver **(not considered related to GvHD)**	Blood bilirubin increase ≥ Grade 2 (caused by increased direct bilirubin) with ALT and/or AST ≥ Grade 2, without evidence of cholestasis and with absence of any alternative cause likely explaining the combination of increased ALT or AST and blood bilirubin
Others	Any other unacceptable non-hematological toxicity encountered by a participant as determined by the Investigators and Novartis
	Grade 3-5 non-hematological toxicity not clearly resulting from the underlying leukemia, inter-current illness, or concomitant medications
	Any AE that leads to study treatment discontinuation if not clearly resulting from the underlying leukemia, inter-current illness, or concomitant medications
	Any treatment-related (non-relapse) death

Exceptions for DLT criteria

- Grade 3 fatigue, asthenia, fever, or constipation
- Grade 3 anorexia, nausea, vomiting, diarrhea not requiring hospitalization, tube feeding or use of total parenteral nutrition (TPN)
- Grade 3 or 4 isolated laboratory abnormalities that last ≤3 days

6.6.4 Dose modifications

For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions, and/or reductions are required in order to allow participants to continue the study treatment.

These dose modifications are summarized in Table 6-9 . Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent discontinuation from study treatment is mandatory for specific events indicated as such in Table 6-9 or listed in Section 6.6.4.

These dose changes must be recorded on the appropriate CRF.

Any final decisions concerning dose modifications or permanently discontinuing the participant from study drug due to study drug related toxicities will occur following a documented discussion with Novartis.

Participants who discontinue the study due to an adverse event or an abnormal laboratory value must be followed as described in Section 9.1.1.

The following general guidelines apply for dose modification (interruption, reduction and/or permanent discontinuation) decision for toxicities (other than GvHD):

- If a participant requires a dose interruption or delay in initiation of a treatment cycle due to toxicities [other than GvHD] for more than 28 consecutive days with siremadlin monotherapy (measured from the intended start date of the new cycle, i.e., from Day 29 of the previous cycle), or more than 42 days for siremadlin/DLI combination cycles (measured from Week 7/Day 43 of the previous cycle), then the participant should be discontinued from the study treatment.
- If a participant experiences an adverse event (AE) meeting the criteria for DLT as outlined in Section 6.6.3 study treatment must be withheld.
- Following resolution of the toxicity to ≤ Grade 1 or to the participant's baseline value prior to worsening of AE, the participant may resume study treatment at the same or a lower dose level (Table 6-9) assessed to be safe, if there is no evidence of hematologic relapse, at the discretion of the treating Investigator.
- If after siremadlin is resumed at a lower dose level, toxicity recurs with the same or worse severity, study treatment (siremadlin) must be discontinued permanently.
- Criteria for dose modification for **adverse drug reactions** are summarized in Table 6-9**.**

Graft-versus-host disease (GvHD) and study treatment dose modification

GvHD following treatment with siremadlin monotherapy (dose confirmation monotherapy in Part 1, priming and/or maintenance phase in Part 2):

- For GvHD [acute (per Harris et al 2016) and/or chronic (per NIH criteria)] meeting DLT definition and/or GvHD requiring systemic anti-GvHD therapy: Interrupt siremadlin.
- Assessment and treatment of GvHD will be at the discretion of the treating physician and per the local standard of practice (see Section 8.4.4.1 and Section 8.4.4.2 for details).
- For acute GvHD ≤ Grade II and/or mild chronic GvHD and/or moderate chronic GvHD excluding lung:
  - If systemic anti-GvHD therapy is not required, maintain siremadlin at the same dose level.
  - If systemic anti-GvHD therapy is required, interrupt siremadlin. Upon improvement of GvHD to ≤ Grade I for acute and/or to ≤ mild for chronic, and persistence of improvement for at least 2 weeks, resuming siremadlin is permitted as monotherapy, at the discretion of the treating investigator at the same dose level.
  - If GvHD symptoms reoccur or worsen following re-initiation of siremadlin requiring systemic anti-GvHD therapy:
    - Interrupt siremadlin.
    - GvHD treatment per the local standard of practice.

    - Upon improvement of GvHD to ≤ Grade I for acute and/or to ≤ mild for chronic, and persistence of improvement for at least 2 weeks, resuming siremadlin is permitted as monotherapy, with a dose modification (decrease by one dose level).
    - If GvHD symptoms reoccur or worsen following re-initiation of siremadlin requiring systemic anti-GvHD therapy: Discontinue siremadlin permanently.
- For acute GvHD Grade III:
    - Interrupt siremadlin.
    - GvHD treatment per the local standard of practice.
    - Upon improvement of acute GvHD to ≤ Grade I, and persistence of improvement for at least 2 weeks, resuming siremadlin is permitted as monotherapy, with a dose modification (decrease by one dose level).
    - If GvHD symptoms reoccur or worsen following re-initiation of siremadlin requiring systemic GvHD therapy: Discontinue siremadlin permanently.
- For acute GvHD Grade IV and/or moderate chronic lung GvHD and/or severe chronic GvHD: Discontinue siremadlin permanently.
- Continuation of systemic anti-GvHD treatment is allowed when resuming siremadlin. Note: Caution with drug-drug interaction between siremadlin and anti-GvHD medications with narrow therapeutic index substrates of CYP3A (e.g. tacrolimus, cyclosporine, sirolimus), and drug level monitoring and dose adjustment must be followed as outlined in Section 6.2.2.1.
- If GvHD occurs following siremadlin monotherapy during **priming phase (Part 2):**
    - For acute GvHD Grade I and/or mild chronic GvHD, participant may proceed to DLI/siremadlin combination phase when all eligibility criteria to receive DLI are met without delay.
    - For acute GvHD Grade II GvHD, DLI/siremadlin combination phase should be delayed and the participant should receive an additional cycle of siremadlin monotherapy before proceeding to DLI/siremadlin combination.
    - In case of development of Grade III/IV acute GvHD and/or moderate/severe chronic GvHD during priming phase, the participant will not be eligible to receive any DLI in combination with siremadlin.

GvHD following treatment with siremadlin/DLI in combination phase (Part 2):

In case of development of GvHD [new onset GvHD of any severity, or worsening of preexisting GvHD from priming phase] during **siremadlin/DLI combination phase**:

- No additional DLI dose(s) should be administered (permanent discontinuation of subsequent DLI).
- Treatment of GvHD will be at the discretion of the treating physician and per the local standard of practice.
- For GvHD (acute or chronic) requiring systemic anti-GvHD therapy: Interrupt siremadlin.
- Following permanent discontinuation of DLI due to development of GvHD, proceeding to maintenance phase with siremadlin monotherapy is permitted, if GvHD has improved to ≤

Grade I for acute and/or to ≤ mild for chronic, and persistence of improvement for at least 2 weeks.

- For acute GvHD ≤ Grade II and/or mild chronic GvHD and/or moderate chronic GvHD excluding lung:
  - Upon improvement of GvHD to ≤ Grade I for acute and/or to ≤ mild for chronic, and persistence of improvement for at least 2 weeks: Proceed to maintenance phase with siremadlin monotherapy at the same dose level.
  - If GvHD symptoms reoccur or worsen following re-initiation of siremadlin requiring systemic anti-GvHD therapy:
    - Interrupt siremadlin.
    - Continue GvHD treatment per the local standard of practice.
    - Upon improvement of GvHD to ≤ Grade I for acute and/or to ≤ mild for chronic, and persistence of improvement for at least 2 weeks, resuming siremadlin is permitted as monotherapy, with a dose modification (decrease by one dose level).
    - If GvHD symptoms reoccur or worsen following re-initiation of siremadlin requiring systemic anti-GvHD therapy: Discontinue siremadlin permanently.
- For acute GvHD Grade III-IV and/or moderate chronic lung GvHD and/or severe chronic GvHD:
  - Upon improvement of GvHD to ≤ Grade I for acute and/or to ≤ mild for chronic, and persistence of improvement for at least 2 weeks: Proceed to maintenance phase with siremadlin monotherapy with a dose modification (decrease by one dose level).
  - If GvHD symptoms reoccur or worsen following re-initiation of siremadlin requiring systemic anti-GvHD therapy: Discontinue siremadlin permanently.
- Continuation of systemic GvHD treatment is allowed when resuming siremadlin. Note: Caution with drug-drug interaction between siremadlin and anti-GvHD medications with narrow therapeutic index substrates of CYP3A (e.g. tacrolimus, cyclosporine, sirolimus), and drug level monitoring and dose adjustment must be followed as outlined in Section 6.2.2.1 .
- Participants who tolerate siremadlin monotherapy re-initiation as the maintenance phase of treatment may continue as planned.

Table 6-9 Criteria for dose reduction / interruption and re-initiation of siremadlin treatment for adverse drug reactions.

Dose modifications for siremadlin	
Worst toxicity CTCAE v5.0 Grade[a]	**Recommended dose modification**
Hematology	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3) and Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain siremadlin dose level without interruption
Grade 3 (ANC <1000 - 500/mm^3)	● Interrupt siremadlin and monitor blood count twice weekly ● When neutropenia is resolved to ≤ Grade 2, resume siremadlin at the same dose level ● Granulocyte-Colony Stimulating Factor (G-CSF)/myeloid growth

	factors may be administered at the discretion of the treating Investigator, in accordance with local standard of practice
Grade 4 (ANC <500/mm^3)	Interrupt siremadlin and monitor blood count twice weekly When neutropenia is resolved to ≤ Grade 2, resume siremadlin with a dose modification (decrease by one dose level) ● G-CSF/myeloid growth factors may be administered at the discretion of the treating Investigator, in accordance with local standard of practice
Grade ≥ 3 febrile neutropenia	● Interrupt siremadlin and monitor blood count twice weekly ● Treatment of febrile neutropenia per local standard of practice ● When neutropenia is resolved to ≤ Grade 2, resume siremadlin with a dose modification (decrease by one dose level) ● G-CSF/myeloid growth factors may be administered at the discretion of the treating Investigator, in accordance with local standard of practice
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3) and Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain siremadlin dose level without interruption
Grade 3 (PLT < 50,000 - 25,000/mm^3) without clinically significant bleeding	● Interrupt siremadlin and monitor blood count twice weekly ● When thrombocytopenia is resolved to ≤ Grade 2, resume siremadlin at the same dose level ● Platelet (PLT) transfusion, supportive care and management of bleeding may be administered at the discretion of the treating Investigator, in accordance with local standard of practice
Grade ≥ 3 thrombocytopenia with clinically significant bleeding	● Interrupt siremadlin and monitor blood count twice weekly ● When thrombocytopenia is resolved to ≤ Grade 2, resume siremadlin with a dose modification (decrease by one dose level) ● Management of bleeding, platelet transfusion and supportive care in accordance with local standard of practice
Grade 4 (PLT < 25,000/mm^3)	Interrupt siremadlin and monitor blood count twice weekly When thrombocytopenia is resolved to ≤ Grade 2, resume siremadlin with a dose modification (decrease by one dose level) ● Platelet transfusion, supportive care and management of bleeding may be administered at the discretion of the treating Investigator, in accordance with local standard of practice
Renal: serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain siremadlin dose level without interruption
Grade 2 (> 1.5 - 3.0 x baseline; > 1.5 – 3.0 x ULN)	● Interrupt siremadlin ● Assess potential etiologies for elevated creatinine in the post-allo-SCT setting. ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, resume siremadlin at the same dose level ● If serum creatinine elevation reoccurs as ≥ Grade 2 after resuming siremadlin: ● Interrupt siremadlin ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, may resume siremadlin with a dose modification (decrease by one dose level)
Grade 3 (> 3.0 x baseline; >3.0 - 6.0 x ULN)	Interrupt siremadlin until resolution to ≤ Grade 1 or baseline value prior to worsening of AE, then resume siremadlin with a dose modification (decrease by one dose level)
Grade 4 (> 6.0 x ULN)	Discontinue siremadlin

Hepatic (not attributed to liver GvHD): Also refer to Table 6-11 and Table 6-12 for follow up of abnormal liver chemistry results.	
Isolated total bilirubin elevation	
Grade 1 (> ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal)	Maintain siremadlin dose level without interruption
Grade 2 (> 1.5 - 3.0 x ULN if baseline was normal; > 1.5 - 3.0 x baseline if baseline was abnormal)	● Interrupt siremadlin ● Repeat liver function tests (LFTs)[b] at least weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or to baseline. ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, resume siremadlin at the same dose level ● If total bilirubin elevation reoccurs as ≥ Grade 2 after resuming siremadlin: ● Interrupt siremadlin ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, may resume siremadlin with a dose modification (decrease by one dose level)
Grade 3 (> 3.0 - 10.0 x ULN if baseline was normal; > 3.0 - 10.0 x baseline if baseline was abnormal)	● Interrupt siremadlin ● Repeat LFTs[b] within 48-72 hours from awareness of the abnormal results, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ Grade 1 or to baseline value prior to worsening of AE ● If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, assess for hemolysis as the etiology per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination) ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, may consider resuming siremadlin with a dose modification after discussion with the Novartis Medical Monitor
Grade 4 (> 10.0 x ULN if baseline was normal; > 10.0 x baseline if baseline was abnormal)*	● Discontinue siremadlin ● Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; then monitor weekly, or as clinically indicated, until resolved to baseline or stabilization over 4 weeks
Isolated AST or ALT elevation	
Grade 1 (> ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal)	Maintain siremadlin dose level without interruption
Grade 2 (> 3.0 - 5.0 x ULN if baseline was normal; > 3.0 - 5.0 x baseline if baseline was abnormal)	● Interrupt siremadlin ● Repeat LFTs[b] at least weekly, or more frequently if clinically indicated, until resolved to ≤ Grade 1 or to baseline ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, resume siremadlin at the same dose level ● If AST or ALT elevation reoccurs as ≥ Grade 2 after resuming siremadlin: ● Interrupt siremadlin ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, may resume siremadlin with a dose modification (decrease by one dose level)
Grade 3 (> 5.0 - 20.0 x ULN if baseline was normal; > 5.0 - 20.0 x baseline if baseline was abnormal)	● Interrupt siremadlin ● Repeat LFTs[b] within 48-72 hours from awareness of the abnormal results, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ Grade 1 or to baseline ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, may consider resuming siremadlin with a dose modification after discussion with the Novartis Medical Monitor

Grade 4 (> 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal)	● Discontinue the treatment ● Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks
Combined [c] elevations of AST or ALT and total bilirubin	
● For participants with normal baseline ALT and AST and total bilirubin value: ● AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis[d] OR ● For participants with elevated baseline AST or ALT or total bilirubin value: ● AST or ALT > 2 x baseline OR > 300 U/L (whichever occurs first) and Total bilirubin > 2 x ULN OR ● AST or ALT > 2 x baseline OR > 300 U/L (whichever occurs first) and Total bilirubin normal or elevated with liver symptoms. **Note: For participants with Gilbert's syndrome, at least 2-fold increase in direct bilirubin.	● Interrupt treatment and assess for potential DILI as a causality ● Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b], or as clinically indicated, until AST, ALT, or total bilirubin have resolved ≤ Grade 1 or to baseline. (Refer to the Section 6.6.5.1 for additional follow-up evaluations as applicable.) ● If DILI (causality indicates drug-related): Permanently discontinue siremadlin ● If not DILI (causality is not related): Treat the identified cause according to institutional guidelines. Once resolved, may resume siremadlin at the same dose level.
Asymptomatic amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN) without symptoms or clinical manifestations of pancreatitis	Maintain siremadlin dose level without interruption
Grade 2 (> 1.5 - 2.0 x ULN; > 2.0 - 5.0 x ULN without symptoms or clinical manifestations of pancreatitis)	● Interrupt siremadlin ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, may resume siremadlin at the same dose level
Grade 3 (> 5.0 x ULN without symptoms or clinical manifestations of pancreatitis)	● Interrupt siremadlin. ● A Computed Tomography (CT) scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within one week of the first occurrence. ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, may resume siremadlin at the same dose level ● If amylase and/or lipase elevation reoccur as ≥ Grade 2 after resuming siremadlin: ● Interrupt siremadlin ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, may resume siremadlin with a dose modification (decrease by one dose level)
Gastrointestinal	
Pancreatitis	
Grade 2	● Interrupt siremadlin ● Manage per institutional practice ● Upon resolution, may resume siremadlin at the same dose level, if no clinical evidence of pancreatitis and after discussion with the Novartis Medical Monitor
Grade ≥ 3	● Interrupt siremadlin ● A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within one week of the first occurrence of Grade ≥ 3

	● If pancreatic pathology or other etiologies have been identified, may consider resuming siremadlin upon resolution, after discussion with the Novartis Medical Monitor
Diarrhea* (not attributed to GI GvHD)**	
Grade 1	● Maintain siremadlin dose level without interruption ● Apply/ modify anti-diarrheal treatment
Grade 2	● Interrupt siremadlin ● Apply/ modify anti-diarrheal treatment per institutional guidelines ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, resume siremadlin at the same dose level. ● If diarrhea reoccurs as ≥ Grade 2: ● Interrupt siremadlin ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, may resume siremadlin with a dose modification(decrease by one dose level)
Grade 3	● Interrupt siremadlin ● Apply/ modify anti-diarrheal treatment per institutional guidelines ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE: ● If resolved within < 3 days of starting anti-diarrhea treatment, resume siremadlin at the same dose level ● If resolved within ≥ 3 days of starting anti-diarrhea treatment, may resume siremadlin with a dose modification (decrease by one dose level)
Grade 4	Discontinue siremadlin
Nausea and/or Vomiting (n/v) (not attributed to GI GvHD)	
Grade 1	● Maintain siremadlin dose level without interruption ● Apply/ modify anti-emetic treatments
Grade 2	● Interrupt siremadlin ● Apply/ modify anti-emetic treatments per institutional guidelines ● Upon resolution of n/v to ≤ Grade 1 or baseline value prior to worsening of AE, resume siremadlin at the same dose level ● If n/v reoccurs as ≥ Grade 2: ● Interrupt siremadlin ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, may resume siremadlin with a dose modification (decrease by one dose level)
Grade 3	● If n/v cannot be controlled with anti-emetic treatments, interrupt siremadlin. ● Upon resolution of n/v to Grade ≤ 1 or baseline value prior to worsening of AE: ● If n/v resolved in < 48 hours, resume siremadlin at the same dose level ● If n/v resolved in ≥ 48 hours, consider resuming siremadlin with a dose modification (decrease by one dose level)
Grade 4	Discontinue siremadlin
Cardiovascular	
ECG QTc-Interval prolonged	
Grade 3 (Average QTc ≥ 501 ms; or > 60 ms change from baseline)	● Interrupt siremadlin ● See Section 6.6.5.2 for evaluation and follow up. ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, may consider resuming siremadlin after discussion with the Novartis Medical Monitor
Grade 4	Discontinue siremadlin

Skin and subcutaneous tissue disorders	
Rash/photosensitivity (excluding acute or chronic skin GvHD by the investigator assessment)	
Grade 1	● Maintain siremadlin dose level without interruption ● Consider initiating appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)
Grade 2	● Continue siremadlin without dose modification ● Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)
Grade 3, despite skin toxicity therapy	● Interrupt siremadlin until resolution to ≤ Grade 1 or baseline value prior to worsening of AE ● Consider Dermatology consultation and skin biopsy to exclude GvHD or other etiologies as clinically appropriate ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE: ● If resolved in ≤ 14 days, resume siremadlin with a dose modification (decrease by one dose level) ● If resolved in > 14 days (despite appropriate skin toxicity therapy): discontinue siremadlin
Grade 4, despite skin toxicity therapy	Discontinue siremadlin
Other adverse events	
Grade 1	Maintain siremadlin dose level without interruption
Grade 2	● Siremadlin interruption may be considered, at Investigator discretion, and if the events are non-manageable by symptomatic therapy ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, resume siremadlin at the same dose level
Grade 3	● Interrupt siremadlin ● Upon resolution to ≤ Grade 1 or baseline value prior to worsening of AE, resuming siremadlin must be discussed with the Novartis Medical Monitor
Grade 4	● Discontinue siremadlin ● If resuming siremadlin is being considered (based on the adverse event, identified etiology, and upon resolution to ≤ Grade 1), it must be discussed with the Novartis Medical Monitor

[a] Common Toxicity Criteria for Adverse Events (CTCAE Version 5.0)
[b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (ALP) (fractionated [quantification of isoforms], if ALP > 2.0 x ULN).
[c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold.
[d] "Cholestasis" defined as ALP elevation (> 2.0 xULN and R value <2) in participants without bone pathology or elevation of ALP liver fraction in participants with bone pathology.
*Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R > 2 and < 5) liver injury.
**Note: Bilirubin can be elevated either as part of a "Hy's law" constellation with a preceding elevation of ALT/AST, or as part of a cholestatic reaction with simultaneous elevation of other cholestatic parameters (ALP, Gamma-glutamyl transferase (GGT)). Isolated bilirubin can be seen in conjunction with treatments that inhibit bilirubin conjugation or excretion. Alternative causes of bilirubin elevation should be ruled out. If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction.
*** Note: Anti-diarrheal medication is recommended at the first sign of abdominal cramping, loose stools, or overt diarrhea.

6.6.5 Follow-up for toxicities

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

Appropriate clinical specialists for specific toxicities, such as cardiologist, gastroenterologist, etc., should be consulted as deemed necessary. All participants must be followed up for adverse events and serious adverse events for 30 days following the last doses of siremadlin.

Table 6-10 outlines the follow-up evaluation recommended for toxicities of specific types and CTCAE grades.

Table 6-10 Follow-up evaluations for selected toxicities

TOXICITY	FOLLOW-UP EVALUATION
Hematologic: Neutropenia ≥ CTCAE grade 3 Thrombocytopenia ≥ CTCAE grade 3	Test twice weekly until ≤ CTCAE grade 2 Continue to test weekly until resolution to baseline or stabilization. Monitor for bleeding and infections.
Pancreatic Amylase or lipase ≥ CTCAE grade 3	Test twice weekly until ≤ CTCAE grade 2. Continue to test weekly until resolution to ≤ CTCAE grade 1 or stabilization. A CT scan or equivalent imaging procedure to assess the pancreas, liver, and gallbladder is recommended within 7 days of the first occurrence of any ≥ CTCAE grade 3 result. In participants with serum triglycerides ≥ 500 mg/dL, urine amylase also needs to be tested.
Cardiac disorders QT and ECG ECG changes indicative of ischemic event	Twice weekly ECGs until normalization or stabilization of ECG findings.

6.6.5.1 Follow up on potential drug-induced liver injury (DILI) cases

Increased transaminases (AST/ALT) combined with increased total bilirubin (TBIL) may be indicative of potentially severe DILI, and should be considered as clinically important events and assessed appropriately to establish the diagnosis.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and TBIL value, as outlined in Table 6-11 and Table 6-12**.**

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury, as follows:

1. A detailed assessment of potential treatment-emergent GvHD of liver (acute or chronic) should be performed by the Investigator.
2. A detailed history, including relevant information, such as cardiac disease, history of any pre-existing liver conditions or risk factors, blood transfusions, IV drug abuse, travel, work, alcohol intake, and full clinical examination for evidence of acute or chronic liver disease, cardiac disease and infection etc. should be performed.

3. Review of concomitant medications, including nonprescription medications and herbal and dietary supplement preparations, alcohol use, recreational drug use, special diets, and chemicals exposed to within one month of the onset of the liver injury.
4. Further testing for acute hepatitis A, B, C or E infection, other hepatotropic viral infection (eg, EBV, CMV, HSV, HHV-6, adenovirus, etc.), and autoimmune hepatitis may be warranted as clinically indicated and per standard of practice post-allo-SCT.
5. Relevant Liver imaging (eg, biliary tract) and liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.
6. Other causes should also be considered based upon participants' medical history (eg, hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, echocardiogram, prior hypotensive episodes; Type 1 diabetes / glycogenic hepatitis).
7. Obtain an unscheduled PK sample, as close as possible to last dose of study treatment, to determine exposure to study treatment and metabolites.

If abnormalities are confirmed, close observation and follow-up are required. Guidelines for follow-up on potential DILI cases are described in Table 6-11 and Table 6-12.

Following appropriate causality assessments, the causality of the treatment is estimated as "probable" ie, >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates probably caused by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria in Table 6-11 and Table 6-12, with no other alternative cause including liver GvHD for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

Criteria for siremadlin dose modification (interruption, re-initiation, dose reduction or permanent discontinuation) for **adverse drug reactions** are listed in Table 6-9.

Table 6-11 Follow-up of abnormal liver chemistry results (not attributed to liver GvHD)

ALT	TBIL	Liver symptoms	Action
ALT increase without bilirubin increase			
• If normal at baseline: ALT > 3 x ULN • If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)	Normal. For participants with Gilbert's syndrome: No change in baseline TBIL	None	• Measure liver function tests (LFTs) [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), TBIL, direct and indirect bilirubin, albumin], prothrombin time (PT)/International Normalized Ratio (INR), lactate dehydrogenase (LDH), creatine kinase (CK), and glutamate

ALT	TBIL	Liver symptoms	Action
			dehydrogenase (GLDH) at least weekly or more frequently if clinically indicated, until resolved to ≤ Grade 1 or to baseline. ● Follow-up for symptoms.
● If normal at baseline: ALT > 5 x ULN for more than two weeks ● If elevated at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal. For participants with Gilbert's syndrome: No change in baseline TBIL	None	● Measure LFTs [ALT, AST, ALP, GGT, TBIL, direct and indirect bilirubin, albumin], PT/INR, LDH, CK, and GLDH within 48-72 hours from awareness of the abnormal results, then monitor weekly or more frequently if clinically indicated, until resolved to ≤ Grade 1 or to baseline or stabilization over 4 weeks. ● Follow-up for symptoms. ● Initiate close monitoring and workup for competing etiologies.
● If normal at baseline: ALT > 8 x ULN	Normal. For participants with Gilbert's syndrome: No change in baseline TBIL	None	
ALT increase with bilirubin increase			
● If normal at baseline: ALT > 3 x ULN ● If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)	TBIL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
● If normal at baseline: ALT > 3 x ULN ● If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 6-12 Action required for isolated total bilirubin elevation

Abnormality	Action required
Any elevation > ULN	Fractionate bilirubin, evaluate for cholestatic liver injury (ALP) or alternative causes of bilirubin elevation. Treat alternative causes according to local institutional guidelines.
Grade 2 (>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal)	Repeat LFTs at least weekly or more frequently if clinically indicated, until resolution to ≤ Grade 1 or to baseline.
Grade 3 (>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal)	Repeat LFTs within 48-72 hours from awareness of the abnormal results, then monitor LFTs weekly or more frequently if clinically indicated, until resolved to ≤ Grade 1 or to baseline.
Grade 4 (>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal)	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks. The participant should be monitored clinically at least weekly or as clinically indicated, until stabilization of bilirubin.

Note: Bilirubin can be elevated either as part of a "Hy's law" constellation with a preceding elevation of ALT/AST, or as part of a cholestatic reaction with simultaneous elevation of other cholestatic parameters (ALP, GGT). Isolated bilirubin can be seen in conjunction with treatments that inhibit bilirubin conjugation or excretion. Alternative causes of bilirubin elevation should be ruled out.

6.6.5.2 Follow up for QTcF Prolongation

In case QTcF > 500 ms (or QTcF prolongation >60 ms from baseline):

- Assess the quality of the ECG recording. Collect two additional ECGs as soon as possible and submit the triplicate for central review.
- A time-matched PK sample for siremadlin should be collected just after the triplicate ECGs are performed due to prolonged QTc, and to record the time and date of the last siremadlin intake to determine the drug exposure.
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia, hypocalcemia). If abnormal, correct abnormalities.
- Review concomitant medication use for possible causes for QT prolongation (refer to crediblemedicines.org). Record all concomitant medications in the appropriate eCRF page.
- Monitor ECG per the institutional standards (e.g. twice weekly ECGs until normalization or stabilization of ECG findings).
- If resuming siremadlin is considered upon resolution to ≤ Grade 1 or baseline, monitor ECGs closely pre- and post-dose (Table 8-11) with a time-matched PK samples at the same time point as ECG taken immediately after ECG (Table 8-12).

6.7 Additional treatment guidance

6.7.1 Treatment compliance

Every time study drug siremadlin is to be administered, IRT must be contacted to register the drug dispensed and/or assign a medication (kit) number.

For study drug taken at home (e.g. for capsules of siremadlin on dosing days participants do not go to the clinic), the investigator must promote compliance by instructing the participant to take the study drugs exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the participant. This information should be captured in the source document at each visit.

DLI will be administered in the clinic or as per local institutional practice.

The date and time of the study treatment administration (siremadlin) and DLI during the study and any deviations from the protocol treatment schedule will be captured by the investigator staff on the appropriate study drug dispensing form. Compliance with the study treatment and any protocol deviations will be assessed by the field monitor on an ongoing basis. All study drug dispensed and returned (if applicable) must be recorded in the Drug Accountability Log.

Pharmacokinetic parameters (measures of siremadlin) will be determined in all participants treated with Siremadlin, as detailed in pharmacokinetics section.

6.7.2 Emergency breaking of assigned treatment code

Not applicable

7 Informed consent procedures

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative (defined as [X]) and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB) . This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study.
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment.
- Patient information sheet for female partners of any male participants who took study treatment.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The Assessment Schedule Table 8-1, Table 8-2, Table 8-3, and Table 8-4 lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen (or contacted during safety and survival follow-up) for all visits/assessments as outlined in the assessment schedule Table 8-1, Table 8-2, Table 8-3, and Table 8-4 or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Each treatment cycle in dose confirmation siremadlin monotherapy (Part 1), priming and maintenance phase (Part 2) is 28 days. Each treatment cycle in combination phase (Part 2) is 42 days. Screening evaluations should be performed within ≤ 28 days of C1D1 (except for the pregnancy test which has to be performed within 72 hours before the first dose).

During the course of the study, visits, test and/or procedures should occur on schedule whenever possible. A visit window of +/- 3 days is allowed for study procedures (including treatment administration). See Section 6.1 for details on study treatment. A window of - 7 days from the planned visit date is allowed for bone marrow aspirate (BMA) procedures before starting siremadlin day 1 of the planned visit. Further, a maximum of +/- 7 days is allowed between BMA efficacy, extramedullary disease assessment (if applicable) and hematology assessments of the same visit except at assessments directly prior to DLI administration (combination phase) which have a maximum window of - 14 days.

Note: If a treatment cycle is delayed at any time during the study, all study visits and safety and efficacy assessments should continue according to the appropriate number of calendar days measured from Day 1 of the previous cycle, or more often if clinically indicated. When treatment is resumed, the first day of study treatment administration will be considered as Day 1 of the new treatment cycle and visit schedule will be shifted accordingly.

On PK collection days the windows are provided in Section 8.5.1 .

Participants who discontinue the study treatment for any reason should be scheduled for an end of treatment (EOT) visit as soon as possible and within 14 days from the decision to permanently discontinue study treatment, at which time all of the assessments listed for the EOT visit will be performed. After discontinuation of study treatment, participants will be followed for post-treatment assessments and survival. During the survival follow-up and post treatment follow-up, a visit window of +/- 14 days is allowed.

For information on post-treatment and survival follow-ups, please refer toSection 9.1.1.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 8-1 Assessment Schedule, Dose confirmation siremadlin monotherapy (Part 1)

Period	Part 1: Siremadlin monotherapy - Cycles duration: 28 days									End of Treatment of dose confirmation phase	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Cycle		Cycle 1				Cycle 2			Cycle 3 (and subsequent cycles, if required)				
Visit Name	SCREENING	CONF C1D1	CONF C1D5	CONF C1D8	CONF C1D15	CONF C2D1	CONF C2D8	CONF C2D15	CONF CxD1	EOT CONF	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	D1	D5	D8	D15	D1	D8	D15	D1	-	30 days after EOT	Every 6 mo until EOS (End of Study)	every 3 mo until EOS
Informed Consent	X												
IRT Registration	X									X			
Demography	X												
Inclusion/ Exclusion criteria	X												
Medical history/current medical conditions[1]	X												
Disease History[2]	X												

Period	**Part 1: Siremadlin monotherapy - Cycles duration: 28 days**									**End of Treatment of dose confirmation phase**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**				**Cycle 2**			**Cycle 3 (and subsequent cycles, if required)**				
Visit Name	**SCREENING**	**CONF C1D1**	**CONF C1D5**	**CONF C1D8**	**CONF C1D15**	**CONF C2D1**	**CONF C2D8**	**CONF C2D15**	**CONF CxD1**	**EOT CONF**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Days	**-28 to -1**	**D1**	**D5**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**-**	**30 days after EOT**	**Every 6 mo until EOS (End of Study)**	**every 3 mo until EOS**
Prior antineoplastic therapies	X												
Prior concomitant medications, surgery and medical procedures	X	Continuous								X	X	X	
Adverse Events	X	Continuous								X	X[3]		
Physical Examination	S	S				S			S	S		S	
Vital Signs	X	X				X			X	X		X	
Body Weight	X	X				X			X	X		X	

Period	**Part 1: Siremadlin monotherapy - Cycles duration: 28 days**									**End of Treatment of dose confirmation phase**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**				**Cycle 2**			**Cycle 3 (and subsequent cycles, if required)**				
Visit Name	**SCREENING**	**CONF C1D1**	**CONF C1D5**	**CONF C1D8**	**CONF C1D15**	**CONF C2D1**	**CONF C2D8**	**CONF C2D15**	**CONF CxD1**	**EOT CONF**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Days	**-28 to -1**	**D1**	**D5**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**-**	**30 days after EOT**	**Every 6 mo until EOS (End of Study)**	**every 3 mo until EOS**
Body Height	X												
ECOG PS	X	X				X			X	X			
Hematology	X	X		X	X	X	X	X	at days 1 & 15 at each cycle until CONF C6 and thereafter every cycle Day 1 and as clinically indicated	X		Every 3 months (starting from last on treatment efficacy assessment) and if clinically indicated	
Chemistry	X	X		X	X	X	X	X	at days 1 & 15 at each cycle until CONF C6 and thereafter every cycle Day 1 and as clinically indicated	X		If clinically indicated	

Period	**Part 1: Siremadlin monotherapy - Cycles duration: 28 days**									**End of Treatment of dose confirmation phase**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**				**Cycle 2**			**Cycle 3 (and subsequent cycles, if required)**				
Visit Name	**SCREENING**	**CONF C1D1**	**CONF C1D5**	**CONF C1D8**	**CONF C1D15**	**CONF C2D1**	**CONF C2D8**	**CONF C2D15**	**CONF CxD1**	**EOT CONF**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Days	**-28 to -1**	**D1**	**D5**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**-**	**30 days after EOT**	**Every 6 mo until EOS (End of Study)**	**every 3 mo until EOS**
Coagulation	X	If clinically indicated											
Cytogenetics[4]	X												
Virology hepatitis B and C	S									If clinically indicated			
HIV serology (only if required per local regulation)	S												
GLDH	X[5]									If clinically indicated			
Acute GvHD assessment[6]	X[6]	X				X			at each cycle until CONF C6D1 and thereafter every 2 cycles and as clinically indicated	X	X	Every 3 months (starting from last on	

Period	**Part 1: Siremadlin monotherapy - Cycles duration: 28 days**									**End of Treatment of dose confirmation phase**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**				**Cycle 2**			**Cycle 3 (and subsequent cycles, if required)**				
Visit Name	**SCREENING**	**CONF C1D1**	**CONF C1D5**	**CONF C1D8**	**CONF C1D15**	**CONF C2D1**	**CONF C2D8**	**CONF C2D15**	**CONF CxD1**	**EOT CONF**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Days	**-28 to -1**	**D1**	**D5**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**-**	**30 days after EOT**	**Every 6 mo until EOS (End of Study)**	**every 3 mo until EOS**
												treatment efficacy assessment) and if clinically indicated	
Chronic GvHD assessment	X[6]	X				X			at each cycle until CONF C6D1 and thereafter every 2 cycles and as clinically indicated	X	X	Every 3 months (starting from last on treatment efficacy assessment) and if clinically indicated[7]	

Period	**Part 1: Siremadlin monotherapy - Cycles duration: 28 days**									**End of Treatment of dose confirmation phase**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**				**Cycle 2**			**Cycle 3 (and subsequent cycles, if required)**				
Visit Name	**SCREENING**	**CONF C1D1**	**CONF C1D5**	**CONF C1D8**	**CONF C1D15**	**CONF C2D1**	**CONF C2D8**	**CONF C2D15**	**CONF CxD1**	**EOT CONF**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Days	**-28 to -1**	**D1**	**D5**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**-**	**30 days after EOT**	**Every 6 mo until EOS (End of Study)**	**every 3 mo until EOS**
Urinalysis (dipstick)	S	If clinically indicated								If clinically indicated			
Serum Pregnancy test [8]	S[9]	S[9]											
Urine Pregnancy Test OR Serum Pregnancy Test[10]						S				S			
12-Lead ECG (triplicates)[11]	X	X	X			If clinically indicated			at CONF C4D1 and if clinically indicated	X			
Echocardiogram or MUGA	X[12]	If clinically indicated							If clinically indicated				

Period	**Part 1: Siremadlin monotherapy - Cycles duration: 28 days**									**End of Treatment of dose confirmation phase**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**				**Cycle 2**			**Cycle 3 (and subsequent cycles, if required)**				
Visit Name	**SCREENING**	**CONF C1D1**	**CONF C1D5**	**CONF C1D8**	**CONF C1D15**	**CONF C2D1**	**CONF C2D8**	**CONF C2D15**	**CONF CxD1**	**EOT CONF**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Days	**-28 to -1**	**D1**	**D5**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**-**	**30 days after EOT**	**Every 6 mo until EOS (End of Study)**	**every 3 mo until EOS**
IRT-Drug dispensation for siremadlin		X				X			X				
Siremadlin administration[13]		X				X			X				
Efficacy - Bone marrow aspirate and/or biopsy	X	D1 of every 3 cycles (starting from C3D1) until completion of 12 cycles of study treatment then every 6 cycles thereafter and as clinically indicated								X[14]		Every 6 mo until relapse or start of new therapy and as clinically indicated. Note: If participant had end of	

Period	Part 1: Siremadlin monotherapy - Cycles duration: 28 days									End of Treatment of dose confirmation phase	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Cycle		Cycle 1				Cycle 2			Cycle 3 (and subsequent cycles, if required)				
Visit Name	SCREENING	CONF C1D1	CONF C1D5	CONF C1D8	CONF C1D15	CONF C2D1	CONF C2D8	CONF C2D15	CONF CxD1	EOT CONF	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	D1	D5	D8	D15	D1	D8	D15	D1	-	30 days after EOT	Every 6 mo until EOS (End of Study)	every 3 mo until EOS
												treatment visit less than 6 months after enrollment, an extra efficacy assessment must be performed at month 3 after EOT	

Period	**Part 1: Siremadlin monotherapy - Cycles duration: 28 days**									**End of Treatment of dose confirmation phase**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**				**Cycle 2**			**Cycle 3 (and subsequent cycles, if required)**				
Visit Name	**SCREENING**	**CONF C1D1**	**CONF C1D5**	**CONF C1D8**	**CONF C1D15**	**CONF C2D1**	**CONF C2D8**	**CONF C2D15**	**CONF CxD1**	**EOT CONF**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Days	**-28 to -1**	**D1**	**D5**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**-**	**30 days after EOT**	**Every 6 mo until EOS (End of Study)**	**every 3 mo until EOS**
Efficacy – extramedullary disease assessment [15]	X	D1 of every 3 cycles (starting from C3D1) until completion of 12 cycles of study treatment then every 6 cycles thereafter and as clinically indicated								X[14]		Every 6 mo until relapse or start of new therapy and as clinically indicated. Note: If participant had end of treatment visit less than 6 months after enrollment, an	

Period	**Part 1: Siremadlin monotherapy - Cycles duration: 28 days**									**End of Treatment of dose confirmation phase**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**				**Cycle 2**			**Cycle 3 (and subsequent cycles, if required)**				
Visit Name	**SCREENING**	**CONF C1D1**	**CONF C1D5**	**CONF C1D8**	**CONF C1D15**	**CONF C2D1**	**CONF C2D8**	**CONF C2D15**	**CONF CxD1**	**EOT CONF**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Days	**-28 to -1**	**D1**	**D5**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**-**	**30 days after EOT**	**Every 6 mo until EOS (End of Study)**	**every 3 mo until EOS**
												extra efficacy assessment must be performed at month 3 after EOT	
Efficacy - response assessment [16]	X[17]	D1 of every 3 cycles (starting from C3D1) until completion of 12 cycles of study treatment then every 6 cycles thereafter and as clinically indicated								X[14]		Every 6 mo until relapse or start of new therapy and as clinically indicated. Note: If	

Period	Part 1: Siremadlin monotherapy - Cycles duration: 28 days									End of Treatment of dose confirmation phase	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Cycle		Cycle 1				Cycle 2			Cycle 3 (and subsequent cycles, if required)				
Visit Name	SCREENING	CONF C1D1	CONF C1D5	CONF C1D8	CONF C1D15	CONF C2D1	CONF C2D8	CONF C2D15	CONF CxD1	EOT CONF	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	D1	D5	D8	D15	D1	D8	D15	D1	-	30 days after EOT	Every 6 mo until EOS (End of Study)	every 3 mo until EOS
												participant had end of treatment visit less than 6 months after enrollment, an extra efficacy assessment must be performed at month 3 after EOT	

Period	**Part 1: Siremadlin monotherapy - Cycles duration: 28 days**									**End of Treatment of dose confirmation phase**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**				**Cycle 2**			**Cycle 3 (and subsequent cycles, if required)**				
Visit Name	**SCREENING**	**CONF C1D1**	**CONF C1D5**	**CONF C1D8**	**CONF C1D15**	**CONF C2D1**	**CONF C2D8**	**CONF C2D15**	**CONF CxD1**	**EOT CONF**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Days	**-28 to -1**	**D1**	**D5**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**-**	**30 days after EOT**	**Every 6 mo until EOS (End of Study)**	**every 3 mo until EOS**
IST levels	X[18]	X[19]	X[19]										
PK sample for siremadlin[20]		X[21]	X[22]						Predose (0h) and 3h postdose PK samples at CONF C4D1, C7D1, C10D1, C13D1, C19D1, and PK profile (see note (20) on C5D1 and C5D5				
[redacted]													

Period	Part 1: Siremadlin monotherapy - Cycles duration: 28 days									End of Treatment of dose confirmation phase	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Cycle		Cycle 1				Cycle 2			Cycle 3 (and subsequent cycles, if required)				
Visit Name	SCREENING	CONF C1D1	CONF C1D5	CONF C1D8	CONF C1D15	CONF C2D1	CONF C2D8	CONF C2D15	CONF CxD1	EOT CONF	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	D1	D5	D8	D15	D1	D8	D15	D1	-	30 days after EOT	Every 6 mo until EOS (End of Study)	every 3 mo until EOS

[redacted]

Period	Part 1: Siremadlin monotherapy - Cycles duration: 28 days									End of Treatment of dose confirmation phase	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Cycle		Cycle 1				Cycle 2			Cycle 3 (and subsequent cycles, if required)				
Visit Name	SCREENING	CONF C1D1	CONF C1D5	CONF C1D8	CONF C1D15	CONF C2D1	CONF C2D8	CONF C2D15	CONF CxD1	EOT CONF	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	D1	D5	D8	D15	D1	D8	D15	D1	-	30 days after EOT	Every 6 mo until EOS (End of Study)	every 3 mo until EOS
[redacted]													

Period	Part 1: Siremadlin monotherapy - Cycles duration: 28 days									End of Treatment of dose confirmation phase	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Cycle		Cycle 1				Cycle 2			Cycle 3 (and subsequent cycles, if required)				
Visit Name	SCREENING	CONF C1D1	CONF C1D5	CONF C1D8	CONF C1D15	CONF C2D1	CONF C2D8	CONF C2D15	CONF CxD1	EOT CONF	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	D1	D5	D8	D15	D1	D8	D15	D1	-	30 days after EOT	Every 6 mo until EOS (End of Study)	every 3 mo until EOS
[redacted]													
Antineoplastic therapies since discontinuation (including a second allo-SCT)											X	X	X

Period	**Part 1: Siremadlin monotherapy - Cycles duration: 28 days**									**End of Treatment of dose confirmation phase**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**				**Cycle 2**			**Cycle 3 (and subsequent cycles, if required)**				
Visit Name	**SCREENING**	**CONF C1D1**	**CONF C1D5**	**CONF C1D8**	**CONF C1D15**	**CONF C2D1**	**CONF C2D8**	**CONF C2D15**	**CONF CxD1**	**EOT CONF**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Days	**-28 to -1**	**D1**	**D5**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**-**	**30 days after EOT**	**Every 6 mo until EOS (End of Study)**	**every 3 mo until EOS**
Collection of disease response status													For participant who received new antineoplastic therapy while in CR/CRi[26]
Survival Follow-up													X
Disposition	X									X		X	

[X] Assessment to be recorded in the clinical database or received electronically from a vendor.
[S] Assessment to be recorded in the source documentation only.
[1] Include allo-SCT and GvHD (acute and chronic) history.
[2] The last assessment of bone marrow and/or peripheral blood counts should be used within 28 days prior to enrollment.

Period	Part 1: Siremadlin monotherapy - Cycles duration: 28 days									End of Treatment of dose confirmation phase	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Cycle		Cycle 1				Cycle 2			Cycle 3 (and subsequent cycles, if required)				
Visit Name	SCREENING	CONF C1D1	CONF C1D5	CONF C1D8	CONF C1D15	CONF C2D1	CONF C2D8	CONF C2D15	CONF CxD1	EOT CONF	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	D1	D5	D8	D15	D1	D8	D15	D1	-	30 days after EOT	Every 6 mo until EOS (End of Study)	every 3 mo until EOS

[3] If the participant begins new antineoplastic medication before the end of the safety follow-up period, then only suspected AEs and suspected SAEs will continue to be collected. See Section 10.1.

[4] To be performed locally. Assessment to be recorded in the clinical database (eCRF).

[5] Refer to Section 6.6.5.1 for DILI follow-up.

[6] If it was performed as part of screening assessment within the previous 7 days, it is not needed to repeat it.

[7] Aligned with the response assessment.

[8] This test will be performed only for women of child-bearing potential.

[9] To be taken at screening and confirmed within 72 hours prior to planned first dose.

[10] Urine or serum test may be performed, depending on local regulations, only for women of child-bearing potential.

[11] Refer to Section 8.4.2 for detailed guidance on timepoints.

[12] A pre-existing assessment may be used (if done within 6 months prior to enrollment).

[13] On days 1 to 5 of each cycle.

[14] This assessment will not be needed at EOT if done at C24D1.

[15] Extramedullary disease is to be assessed via physical examination. Additional evaluation [eg, imaging, procedures (tissue biopsy, lumbar puncture), etc.] will be performed as clinically indicated per the investigator's assessment.

[16] See Section 8.3.1 for details on response assessment.

[17] A pre-existing assessment done as part of standard of care can be used, if done within 28 days of start of study treatment for bone marrow and peripheral blood counts (within 14 days of start of study treatment.

Period	Part 1: Siremadlin monotherapy - Cycles duration: 28 days									End of Treatment of dose confirmation phase	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Cycle		Cycle 1				Cycle 2			Cycle 3 (and subsequent cycles, if required)				
Visit Name	SCREENING	CONF C1D1	CONF C1D5	CONF C1D8	CONF C1D15	CONF C2D1	CONF C2D8	CONF C2D15	CONF CxD1	EOT CONF	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	D1	D5	D8	D15	D1	D8	D15	D1	-	30 days after EOT	Every 6 mo until EOS (End of Study)	every 3 mo until EOS

[18] Report the last IST level measurements within 7 to 9 days before starting siremadlin.
[19] IST level to be measured prior to siremadlin administration
[20] Refer to appropriate table of Section 8.5.1.1 for detailed timepoints and collection schedule for siremadlin PK sampling.
[21] Sampling to be performed at pre-dose of siremadlin, and 0.5h, 1h, 2h, 3h, 6h, 8h, 10h, and 24h post-dose.
[22] Sampling to be performed at pre-dose of siremadlin, and 0.5h, 1h, 2h, 3h, 6h, and 8h post-dose.
[redacted]
[26] New anti-neoplastic therapy includes second allo-SCT see Section 9.1.1.3 for more details. The visit can either be via phone call or on-site (if participant happens to be visiting the site).

Table 8-2 Assessment Schedule, Overview (Part 2)

Period	Pre-Treatment	Treatment			End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Visit Name	Screening	Priming	Combination	Maintenance	End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	Ref to Table 8-3	Ref to Table 8-4	Ref to Table 8-4	EOT	30 days after EOT	Every 6 mo after EOT	every 3 mo until EOS
Informed consent	X							
IRT Registration	X				X			
Demography	X							
Inclusion / Exclusion criteria	X							
Medical history/current medical conditions[1]	X							
Disease History[2]	X							
Prior antineoplastic therapies	X							
Prior/concomitant medications, surgery and medical procedures	X				X	X	X	
Adverse Events	X				X	X[3]		
Physical Examination	S				S		S	
Vital Signs	X				X		X	
Body Height	X							
Body Weight	X				X		X	
ECOG PS	X				X			
Acute GvHD assessment	X				X	X	Every 3 months (starting from last on treatment	

Period	Pre-Treatment	Treatment			End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Visit Name	Screening	Priming	Combination	Maintenance	End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	Ref to Table 8-3	Ref to Table 8-4	Ref to Table 8-4	EOT	30 days after EOT	Every 6 mo after EOT	every 3 mo until EOS
							efficacy assessment) and if clinically indicated [4]	
Chronic GvHD assessment	X				X	X	Every 3 months (starting from last on treatment efficacy assessment) and if clinically indicated [4]	
Hematology	X				X		Every 3 months (starting from last on treatment efficacy assessment) and if clinically indicated	
Chemistry	X				X		If clinically indicated	
Coagulation	X				If clinically indicated			
Cytogenetics [5]	X							
Urinalysis (dipstick)	S				If clinically indicated			
Virology hepatitis B and C	S				If clinically indicated			
HIV serology (only if required per local regulation)	S							
GLDH	X[6]				If clinically indicated			
Serum Pregnancy test [7]	S[8]				S			

Period	Pre-Treatment	Treatment			End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Visit Name	Screening	Priming	Combination	Maintenance	End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	Ref to Table 8-3	Ref to Table 8-4	Ref to Table 8-4	EOT	30 days after EOT	Every 6 mo after EOT	every 3 mo until EOS
Urine Pregnancy Test OR Serum Pregnancy Test[9]						S		
12-Lead ECG (triplicates)[10]	X				X			
Echocardiogram or MUGA	X[11]				If clinically indicated			
Efficacy - Bone marrow aspirate and/or biopsy	X	D1 of every 3 cycles (starting from C3D1) until completion of 12 cycles of study treatment then every 6 cycles thereafter and as clinically indicated			X[12]		Every 6 mo until relapse or start of new therapy and as clinically indicated. Note: If participant had end of treatment visit less than 6 months after enrollment, an extra efficacy assessment must be performed at month 3 after EOT	
Efficacy - extramedullary disease assessment[13]	X	D1 of every 3 cycles (starting from C3D1) until completion of 12 cycles of study treatment then every 6 cycles thereafter and as clinically indicated			X[12]		Every 6 mo until relapse or start of new therapy and as clinically indicated. Note: If participant had end of treatment visit less than 6 months after enrollment, an extra efficacy assessment must be performed at month 3 after EOT	
Efficacy - response assessment[14]	X[15]	D1 of every 3 cycles (starting from C3D1) until completion of 12 cycles of study treatment then every 6 cycles thereafter and as clinically indicated			X[12]		Every 6 mo until relapse or start of new therapy and as clinically indicated. Note: If participant had end of treatment visit less than 6 months after enrollment, an extra efficacy assessment	

Period	Pre-Treatment	Treatment			End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Visit Name	Screening	Priming	Combination	Maintenance	End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	Ref to Table 8-3	Ref to Table 8-4	Ref to Table 8-4	EOT	30 days after EOT	Every 6 mo after EOT	every 3 mo until EOS
							must be performed at month 3 after EOT	
IST level	X[16]	X[17]						
[redacted]								
Antineoplastic therapies since discontinuation (including a second allo-SCT)						X	X	X
Disposition	X				X		X	
Collection of disease response status								For participant who received new

Period	Pre-Treatment	Treatment			End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Visit Name	Screening	Priming	Combination	Maintenance	End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Days	-28 to -1	Ref to Table 8-3	Ref to Table 8-4	Ref to Table 8-4	EOT	30 days after EOT	Every 6 mo after EOT	every 3 mo until EOS
								antineoplastic therapy while in CR/CRi20
Survival Follow-up								X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Include allo-SCT and GvHD (acute and chronic) history
[2] The last assessment of bone marrow and/or peripheral blood counts should be used within 28 days prior to enrollment
[3] If the participant begins new antineoplastic medication before the end of the safety follow-up period, then only suspected AEs and suspected SAEs will continue to be collected. See Section 10.1
[4] Aligned with the response assessment
[5] To be performed locally. Assessment to be recorded in the clinical database (eCRF)
[6] Refer to Section 6.6.5.1 for DILI follow-up.
[7] This test will be performed only for women of child-bearing potential.
[8] To be taken at screening and confirmed within 72 hours prior to planned first dose
[9] Urine or serum test may be performed, depending on local regulations, only for women of child-bearing potential
[10] Refer to Section 8.4.2 for detailed guidance on timepoints
[10] A pre-existing assessment may be used (if done within 6 months prior to enrollment)
[12] This assessment will not be needed at EOT if done at C24D1.
[13] Extramedullary disease is to be assessed via physical examination. Additional evaluation [eg, imaging, procedures (tissue biopsy, lumbar puncture), etc.] will be performed as clinically indicated per the investigator's assessment
[14] See Section 8.3.1 for details on response assessments
1[5] A pre-existing assessment done as part of standard of care can be used, if done within 28 days of start of study treatment for bone marrow and peripheral blood counts (within 14 days of start of study treatment .
[16] Report the last IST level measurements within 7 to 9 days before starting siremadlin
[17] IST level to be measured prior to siremadlin administration
[redacted]
[20] New anti-neoplastic therapy includes second allo-SCT. The visit can either be via phone call or on-site (if participant happens to be visiting the site)

Table 8-3 Assessment Schedule, Priming (Part 2)

Period	**Priming (PRIM) - Cycles duration: 28 days**										**End of Priming phase disposition**
Cycle	**Cycle 1**					**Cycle 2**				**Cycle 3 (and subsequent cycles, if required)**	
Visit Name	**PRIM C1D1**		**PRIM C1D5**	**PRIM C1D8**	**PRIM C1D15**	**PRIM C2D1**		**PRIM C2D8**	**PRIM C2D15**	**PRIM CxD1**	**EO PRIM Disposition**
Days	**D1**		**D5**	**D8**	**D15**	**D1**		**D8**	**D15**	**D1**	**-**
Comments											For patients moving to combination therapy, see Table 8-4
concomitant medications, surgery and medical procedures		Continuous									
Adverse Events		Continuous									
Physical Examination	S					S				S	
Vital Signs	X					X				X	
Body Weight	X					X				X	
ECOG PS	X					X				X	
Hematology	X			X	X	X		X	X	at days 1 & 15 at each cycle until PRIM C6 and thereafter every cycle Day 1 and as clinically indicated	
Chemistry	X			X	X	X		X	X	at days 1 & 15 at each cycle until PRIM C6 and thereafter every cycle Day 1and as clinically indicated	
Coagulation		If clinically indicated				If clinically indicated					
Acute GvHD assessment	X[1]					X				at each cycle until PRIM C6D1 and thereafter every 2 cycles and as clinically indicated	
Chronic GvHD assessment	X[1]					X				at each cycle until PRIM C6D1 and thereafter every 2 cycles and as clinically indicated	
Urinalysis (dipstick)		If clinically indicated									

Period	**Priming (PRIM) - Cycles duration: 28 days**										**End of Priming phase disposition**
Cycle	**Cycle 1**					**Cycle 2**				**Cycle 3 (and subsequent cycles, if required)**	
Visit Name	**PRIM C1D1**		**PRIM C1D5**	**PRIM C1D8**	**PRIM C1D15**	**PRIM C2D1**		**PRIM C2D8**	**PRIM C2D15**	**PRIM CxD1**	**EO PRIM Disposition**
Days	**D1**		**D5**	**D8**	**D15**	**D1**		**D8**	**D15**	**D1**	**-**
Serum Pregnancy test [2]	S[3]										
Urine Pregnancy Test OR Serum Pregnancy Test[4]						S				S	
12-Lead ECG (triplicates)[5]	X		X			If clinically indicated				at PRIM C4D1 and if clinically indicated	
Echocardiogram or MUGA	If clinically indicated										
IST level	X[6]		X[6]								
IRT-Drug dispensation for siremadlin	X					X				X	
Siremadlin administration[7]	X					X				X	
Efficacy assessments									Refer to Table 8-2 for detailed assessments and schedule		
PK sample for siremadlin[8]	X[9]		X[10]							Predose (0h) and 3h postdose PK samples at PRIM C4D1, C7D1, C10D1, C13D1, C19D1, and PK profile (see note 10) on C5D1 and C5D5	

[redacted]

Period	**Priming (PRIM) - Cycles duration: 28 days**										**End of Priming phase disposition**
Cycle	**Cycle 1**					**Cycle 2**				**Cycle 3 (and subsequent cycles, if required)**	
Visit Name	**PRIM C1D1**		**PRIM C1D5**	**PRIM C1D8**	**PRIM C1D15**	**PRIM C2D1**		**PRIM C2D8**	**PRIM C2D15**	**PRIM CxD1**	**EO PRIM Disposition**
Days	**D1**		**D5**	**D8**	**D15**	**D1**		**D8**	**D15**	**D1**	**-**
Disposition											Participants can go either to Combination phase or to End of Treatment

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] If it was performed as part of screening assessment within the previous 7 days, it is not needed to repeat it
[2] This test will be performed only for women of child-bearing potential
[3] To be performed only if it was not done in screening within 72 hours before first dose
[4] Urine or serum test may be performed, depending on local regulations, only for women of child-bearing potential
[5] Refer to Section 8.4.2 for detailed guidance on timepoints
[6] IST level to be measured prior to siremadlin administration
[7] On days 1 to 5 of each cycle
[8] Refer to appropriate table of Section 8.5.1.1 for detailed timepoints and collection schedule for siremadlin PK sampling.
[9] Sampling to be performed at pre-dose of siremadlin, and 0.5h, 1h, 2h, 3h, 6h, 8h, 10h, and 24h post-dose
[10] Sampling to be performed at pre-dose of siremadlin, and 0.5h, 1h, 2h, 3h, 6h, and 8h post-dose
[redacted]

Table 8-4 Assessment Schedule, Combination and Maintenance (Part 2)

Period	**Combination (COMB) - Cycles duration: 42 days**											**End of Combination phase disposition**	**Maintenance (MAINT) - Cycles duration: 28 days**		
Cycle	**Cycle 1**				**Cycle 2**			**Cycle 3**					**Cycle 1**		**Cycle 2 (and subsequent cycles)**
Visit Name	**COMB C1D1**	**COMB C1D3**	**COMB C1D5**	**COMBC1 D15**	**COMB C2D1**	**COMB C2D3**	**COMBC2 D15**	**COMB C3D1**	**COMB C3D3**	**COMB C3D5**	**COMB C3D15**	**EO COMB Disposition**	**MAINT C1D1**	**MAINT C1D5**	**MAINT CxD1**
Days	**D1**	**D3**	**D5**	**D15**	**D1**	**D3**	**D15**	**D1**	**D3**	**D5**	**D15**	**-**	**D1**	**D5**	**D1**
concomitant medications, surgery and medical procedures	Continuous														
Adverse Events	Continuous														
Physical Examination	S				S			S					S		S
Vital Signs	X				X			X					X		X
Body Weight	X				X			X					X		X
ECOG PS	X				X			X					X		X
Hematology	X			X	X		X	X			X		X		X
Chemistry	X			X	X		X	X			X		X		At MAINT C2D1, C3D1 and every 3 cycles thereafter
Coagulation	If clinically indicated														
Acute GvHD assessment	X				X			X					X		At MAINT C2D1, C3D1 and every 3 cycles thereafter and as clinically indicated

Period	**Combination (COMB) - Cycles duration: 42 days**											**End of Combination phase disposition**	**Maintenance (MAINT) - Cycles duration: 28 days**		
Cycle	**Cycle 1**				**Cycle 2**			**Cycle 3**					**Cycle 1**		**Cycle 2 (and subsequent cycles)**
Visit Name	**COMB C1D1**	**COMB C1D3**	**COMB C1D5**	**COMBC1 D15**	**COMB C2D1**	**COMB C2D3**	**COMBC2 D15**	**COMB C3D1**	**COMB C3D3**	**COMB C3D5**	**COMB C3D15**	**EO COMB Disposition**	**MAINT C1D1**	**MAINT C1D5**	**MAINT CxD1**
Days	**D1**	**D3**	**D5**	**D15**	**D1**	**D3**	**D15**	**D1**	**D3**	**D5**	**D15**	**-**	**D1**	**D5**	**D1**
Chronic GvHD assessment	X				X			X					X		At MAINT C2D1, C3D1 and every 3 cycles thereafter and as clinically indicated
Urinalysis (dipstick)	If clinically indicated														
Urine Pregnancy Test OR Serum Pregnancy Test[1]	S				S			S					S		S
12-Lead ECG (triplicates)	X[2]														
Echocardiogram or MUGA	If clinically indicated														
IRT-Drug dispensation for siremadlin	X				X			X					X		X
Siremadlin administration[3]	X				X			X					X	X	X

Period	Combination (COMB) - Cycles duration: 42 days											End of Combination phase disposition	Maintenance (MAINT) - Cycles duration: 28 days		
Cycle	Cycle 1				Cycle 2			Cycle 3					Cycle 1		Cycle 2 (and subsequent cycles)
Visit Name	COMB C1D1	COMB C1D3	COMB C1D5	COMBC1 D15	COMB C2D1	COMB C2D3	COMBC2 D15	COMB C3D1	COMB C3D3	COMB C3D5	COMB C3D15	EO COMB Disposition	MAINT C1D1	MAINT C1D5	MAINT CxD1
Days	D1	D3	D5	D15	D1	D3	D15	D1	D3	D5	D15	-	D1	D5	D1
DLI administration		X				X			X						
Efficacy assessments	Refer to Table 8-2 for details on assessments and schedule														
Efficacy - Bone marrow aspirate and/or biopsy[4]	X[5]												X[6]		D1 of every 3 cycles (starting from Maint C3D1) until completion of 12 cycles of study treatment then every 6 cycles thereafter and as clinically indicated
Efficacy - extramedullary disease assessment[4,7]	X[5]												X[6]		D1 of every 3 cycles (starting Maint C3D1) until completion of 12 cycles of study treatment then every 6 cycles thereafter and as clinically indicated
Efficacy - response assessment[4,8]	X[5]												X[6]		D1 of every 3 cycles (starting from Maint C3D1) until completion of 12 cycles of study treatment then every 6 cycles thereafter and as clinically indicated
PK sample for siremadlin[9]	X[10]		X[10]					X[10]		X[10]			X[10]	X[10]	At MAINT C4D1, C7D1, C10D1, C13D1, and C19D1

Period	Combination (COMB) - Cycles duration: 42 days											End of Combination phase disposition	Maintenance (MAINT) - Cycles duration: 28 days		
Cycle	Cycle 1				Cycle 2			Cycle 3					Cycle 1		Cycle 2 (and subsequent cycles)
Visit Name	COMB C1D1	COMB C1D3	COMB C1D5	COMBC1 D15	COMB C2D1	COMB C2D3	COMBC2 D15	COMB C3D1	COMB C3D3	COMB C3D5	COMB C3D15	EO COMB Disposition	MAINT C1D1	MAINT C1D5	MAINT CxD1
Days	D1	D3	D5	D15	D1	D3	D15	D1	D3	D5	D15	-	D1	D5	D1
[redacted]															
Disposition												X			

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Urine or serum test may be performed, depending on local regulations, only for women of child-bearing potential
[2] To be performed only if participant entered combination prior to completion of cycle 4 in Priming. Refer to Section 8.4.2 for detailed guidance on timepoints
[3] On days 1 to 5 of each cycle
[4] Assessment to be performed prior to DLI administration - protocol allows a 14 days window for efficacy assessments [redacted].
[5] If the bone marrow assessment was performed at last cycle (in priming phase), this assessment may be postponed to the third cycle of the combination phase (to maintain the frequency of BMA/BMB every 3 cycles).
[6] If the bone marrow assessment was performed at last cycle (in combination phase), this assessment may be postponed to the third cycle of the maintenance phase (to maintain the frequency of BMA/BMB every 3 cycles)
[7] Extramedullary disease is to be assessed via physical examination. Additional evaluation [eg, imaging, procedures (tissue biopsy, lumbar puncture), etc.] will be performed as clinically indicated per the investigator's assessment
[8] See Section 8.3.1 for details on response assessments
[9] Refer to appropriate table of Section 8.5.1.1 for detailed timepoints and collection schedule for siremadlin PK sampling.
[10] Sampling to be performed at pre-dose, 0.5h, 1h, 2h, 3h, 6h, and 8h post-dose at this specific time point.
[redacted]

8.1 Screening

All participants must provide signed ICFs prior to performing any study specific procedures. Participants will be evaluated against all study inclusion and exclusion criteria.

After signing the ICFs, screening assessments should be completed within 28 days prior to the start of study treatment (C1D1), with the exception of the local serum pregnancy test (for women of child-bearing potential) which must be conducted and confirmed as negative within 72 hrs prior to the start of study treatment. Laboratory parameters may be retested within the 28-day screening period. If the repeat value remains outside of the specified ranges, the participant will be considered a screen failure.

Re-screening should only occur after a participant has failed screening. An individual participant may only be re-screened once for the study. Participant will need to be re-consented and a new ICF will need to be signed if the investigator chooses to re-screen the participant. Any re-screened participant should receive a new participant No., and the original participant number must be noted on the Re-Screening CRF. All required screening activities must be performed when the participant is re-screened for participation in the study.

8.1.1 Eligibility screening

Following registering in the IRT for screening, participant eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE Section 10.1.3 for reporting details).

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition Case Report Form.

8.2 Participant demographics/other baseline characteristics

Demographics and other baseline characteristics data to be collected on all participants include:

- Relevant medical history and current medical conditions
- Disease (AML) history, including
  - Date of initial diagnosis and date of disease relapse(s).
  - 2016 World Health Organization (WHO) AML classification (Arber et al 2016).
  - From initial diagnosis: ELN cytogenetic risk stratification (Döhner et al 2017), and any additional molecular markers (FLT3-TKD, isocitrate dehydrogenase 1 and 2 (IDH1/2),

DNMT3A, c-KIT, and others) (National Comprehensive Cancer Network (2021)). Refer to Appendix 5 Section 16.5 for details.

- For participants who received allo-SCT in CR2 or greater: In addition to ELN cytogenetic risk stratification (Döhner et al 2017), and any additional molecular markers (FLT3-TKD, isocitrate dehydrogenase 1 and 2 (IDH1/2), DNMT3A, c-KIT, and others), collect data on the latest results of cytogenetics and molecular markers that were last performed prior to allo-SCT. Refer to Appendix 5 Section 16.5 for details.

- Prior antineoplastic therapies [prior to and post-allo-SCT (before start of study treatment)].
- Allo-SCT characteristics, conditioning regimen intensity, disease remission status at transplant (e.g., CR with undetectable MRD, CR with detectable MRD), timing of transplant (e.g., CR1, ≥CR2), prior and current history of acute GvHD or chronic GvHD, prior and current immunosuppressive therapy (systemic GvHD prophylaxis or treatment) and date of completion).
- Race/ethnicity (in order to allow for signal detection and racial/ethnic sensitivity reports required for registration in multiple countries).
- All prior and concomitant medications and medical procedure must be documented. All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, we need to assess the diversity of the study population as required by Health Authorities.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the participant's eCRF.

Other assessments will be completed for the purpose of determining eligibility for inclusion in the study as reported in Section 5.

Assessments to be performed at screening include:

- Physical examination.
- ECOG Performance Status, body height, weight, vital signs (blood pressure (supine position preferred when ECGs are collected) and pulse, and body temperature).
- Laboratory: hematology, chemistry, coagulation, urinalysis, serum pregnancy test for women of child-bearing potential, virology hepatitis B and C, HIV serology (only if required per local regulation), GLDH.

If multiple laboratory tests were performed during screening to confirm eligibility, the lab values closest to enrollment (C1D1 visit) should be used (last available values during screening).

- Triplicate 12-lead central ECG.

- Echocardiogram (or MUGA- Multiple gated acquisition) unless it was performed within 6 months of enrollment.
- Cytogenetics.
- Bone marrow biopsy / aspirate and peripheral blood to establish the diagnosis. If a bone marrow aspirate or biopsy was conducted during the regular work-up of the participant and falls within 28 days prior to the first dose of study treatment (C1D1 visit) (although prior to signing main study ICF), it may be considered as the baseline assessment for the study. Any deviation from this timelines needs to be confirmed with Novartis.
- CT Scan/MRI if extramedullary disease is present or suspected.
- [redacted]

Blood samples for PK will be taken during screening in order to perform the required IST tapering (ref to Section 6.2.2.1 for details).

8.3 Efficacy

Efficacy / disease response assessments will be performed locally, by the Investigator assessment, according to the schedule depicted in Table 8-1, Table 8-2, Table 8-3, and Table 8-4.

8.3.1 Efficacy - Disease status assessment

The study primary efficacy endpoint is measured by the proportion of participants who are alive and maintained CR or CRi with no evidence of hematologic relapse (per investigator assessment) over at least 6 months after start of study treatment (siremadlin monotherapy, as priming and/or maintenance, with or without siremadlin in combination with DLI).

Disease response assessment will be according to the European LeukemiaNet (ELN) AML recommendations (Döhner et al 2017) and International Working Group (IWG) AML response criteria (Cheson et al 2003).

Disease status evaluation at baseline and efficacy assessment during study treatment consist of evaluation of bone marrow aspirate (BMA)/bone marrow biopsy (BMB), peripheral blood (PB), hematology assessments and extramedullary disease assessments. Disease status assessment will be either complete remission, complete remission with incomplete hematologic recovery, or hematologic relapse.

Bone marrow assessments will be performed as outlined in Table 8-1 and in Table 8-2 at screening, and on D1 (pre-dose of study treatment) of every 3 cycles until completion of 12 cycles of study treatment (since study entry) then every 6 cycles thereafter (+/- 14 days) and as clinically indicated.

After the EOT, bone marrow assessments will be performed every 6 months and as clinically indicated until relapse, start of a new anti-neoplastic treatment, death, lost to follow-up or withdrawal of consent.

Additional (unscheduled) bone marrow assessments may be performed as clinically indicated.

Bone marrow and peripheral blood pathology specimens (i.e. bone marrow aspirate slides, bone marrow biopsy block if applicable, peripheral blood smears) prepared locally for the disease response assessment should be sent to the Novartis designated central laboratory for storage. This includes specimens taken during the regular work-up of the participant and used as baseline assessment for the study as mentioned in Section 8.2. A copy of the corresponding pathology reports should be collected and sent to the Novartis designated central laboratory for storage. Central morphology review of the pathology specimens may be performed, if deemed necessary.

Hematology assessments will be performed at screening, and pre-dose at D1 of each cycle (in dose confirmation, priming, combination and maintenance phase), at the end of treatment visit, at unscheduled visit as clinically indicated, and every 3 months for participants who enter post-treatment follow-up.

In case of missing data for the full assessment required to qualify for a given response, the overall assessment “unknown” will be assigned unless relapse was seen in at least one compartment (i.e. bone marrow or blood, or appearance of extramedullary disease).

Disease status evaluation at baseline: the last assessment of bone marrow (within 28 days of start of study treatment) and peripheral blood counts as well as extramedullary disease assessment (within 14 days of start of study treatment) at the screening visit may be used. Any disease response assessments obtained after start of study treatment (C1D1 and beyond) cannot be considered baseline assessment.

Extramedullary disease assessment: is performed primarily via physical examination. Additional evaluation for extramedullary disease [eg, imaging, procedures (tissue biopsy, lumbar puncture), etc.] will be performed as clinically indicated per the investigator's assessment. Cerebrospinal fluid assessment and relevant imaging techniques may be performed, as clinically appropriate at the investigator's discretion, in case of symptoms suggestive of meningeosis leukemia, and/or prior history of central nervous system involvement with AML. In case of appearance or reappearance of extramedullary disease during the study, the lesions should be considered for confirmation by imaging or biopsy if technically and/or clinically feasible.

Assessment for the presence or absence of extramedullary disease will be performed at a similar schedule as the bone marrow assessment and should be performed prior to the first cycle of the siremadlin/DLI combination.

The presence or absence and physical location of extramedullary disease are to be recorded on the CRFs.

Participants can be assessed for disease response (bone marrow assessment, hematology, extramedullary disease assessment) at any time if clinically indicated, for example in case of suspicion of relapse. Therefore, more frequent efficacy assessments may be performed at the

investigator's discretion, if medically indicated, and should be recorded on the Unscheduled Visit eCRFs. All scheduled and unscheduled assessments will be analyzed.

Clinical suspicion of relapse at any time will require an evaluation promptly, rather than waiting for the next scheduled assessment.

In case of an unscheduled or delayed disease evaluation of any reason, subsequent assessments should be performed according to the originally planned schedule.

Table 8-5 Response classification in AML at a given evaluation time (based on IWG Cheson et al 2003, ELN 2017 Döhner et al 2017)

Response Category	Definition[1]
Complete remission (CR)	● Bone marrow: blasts < 5% ● Peripheral blood: No circulating blasts or blasts with Auer rods ● No evidence of extramedullary disease (such as Central Nervous System (CNS) or soft tissue involvement) ● Neutrophils ≥ $1.0x10^9$/L ● Platelets ≥ $100x10^9$/L
Complete remission with incomplete hematologic recovery (CRi)	● Bone marrow: blasts < 5% ● Peripheral blood: No circulating blasts or blasts with Auer rods ● No evidence of extramedullary disease (such as CNS or soft tissue involvement) ● Neutrophils < $1.0x10^9$/L or platelets < $100x10^9$/L
Hematologic relapse (from CR or CRi)	Only in participants with CR or CRi. Any of the following: ● Reappearance of blasts in peripheral blood **OR** ● Bone marrow blasts ≥ 5% **OR** ● Development of extramedullary disease
Unknown	In case the response assessment was not done or the assessment was incomplete

[1] If not defined otherwise, all of these criteria apply.

8.3.2 Appropriateness of efficacy assessments

The assessment of response to study treatment is based on standardized criteria as proposed by the European LeukemiaNet (ELN) and the International Working Group (IWG) (Cheson et al 2003, Döhner et al 2017) in Table 8-5.

8.4 Safety

Safety assessments are specified below in Table 8-6 with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-6 Assessments and Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination is required at D1 of each cycle.Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent, which meet the definition of an Adverse Event, must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.
Height and weight	Height in centimeters (cm) will be measured at Screening. Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at screening and at subsequent timepoints as specified in Table 8-1; Table 8-2; Table 8-3; and Table 8-4

Performance status:

ECOG Performance status scale will be used as described in Table 8-7.

Table 8-7 ECOG performance status

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

8.4.1 Laboratory evaluations

Local clinical laboratory parameters will be used for the analysis of scheduled hematology, chemistry and other blood specimens collected as part of safety monitoring (as detailed in Table 8-1; Table 8-2; Table 8-3; Table 8-4 and Table 8-8; Table 8-9) and the results will be collected in the eCRF.

Unscheduled assessments of these parameters can be performed more often as clinically indicated. It is preferable to use the same laboratory for all the assessments performed, especially for the hematology assessments.

A central laboratory will be used for the parameters listed in Table 8-9 and as per the schedule in Table 8-1; Table 8-2; Table 8-3, and Table 8-4.

Laboratory values obtained during the Screening phase will be used to assess participant's eligibility.

Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for all local laboratories used to the trial.

As per Section 4.6, during a public health emergency as declared by local or regional authorities' i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Table 8-8 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin (Hgb), Leucocytes, Platelets, Erythrocyte Cell Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, metamyelocytes, myelocytes, promyelocytes, blasts, Other), (absolute value preferred, %s are acceptable), atypical cells (e.g. Large unstained cells (LUC), erythroblasts)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphate, Sodium, Potassium, Creatinine, Creatine kinase, (Direct Bilirubin, Indirect Bilirubin)*, eGFR, Total Bilirubin, Total Cholesterol, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting)
Virology**	HBsAg, HBcAb, HBV DNA (in participants positive for HBcAb), HCV RNA (PCR-Polymerase Chain Reaction) HIV (Only if required by local regulation)
Urinalysis**	Dipstick examination includes specific gravity, pH, glucose, protein, blood, bilirubin, ketones and WBC as clinically indicated. If urinalysis dipstick shows abnormalities, the site should perform a more detailed urinalysis follow-up as clinically indicated and per local practice.
Coagulation	International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Pregnancy** Test	Serum / Urine pregnancy test (refer to Section 8.4.3 'Pregnancy and assessments of fertility')

* Indirect and direct bilirubin only required if total bilirubin is abnormal
** Virology, urinalysis, and pregnancy test will only be reported in the source documentation

Table 8-9 Central clinical laboratory parameters collection plan

Test Category	Test Name
Chemistry for DILI[1]	Glutamate dehydrogenase (GLDH)

[1] at baseline and as clinically indicated for follow-up of DILI per Section 6.6.5.1

8.4.2 Electrocardiogram (ECG)

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, blood sampling, and any remaining assessments for that visit (refer to flow diagram below).

Figure 8-1 Timing of study procedures

The ECG are to be collected with ECG machines supplied by the central ECG vendor at the timepoints indicated in the ECG collection plan (Table 8-10 and Table 8-11) and transmitted to the central ECG vendor to be centrally reviewed by an independent reviewer. Full details of all

procedures relating to the ECG collection and reporting will be contained in the technical manual, which is provided to the site by the ECG vendor. Any original ECG not transmitted electronically to the central ECG vendor should be forwarded for central review. Any identifier details must be redacted e.g. participant initials, date of birth as per local regulations.

Triplicate 12 lead ECGs are to be recorded approximately 2 minutes apart. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each participant. The Fridericia QT correction formula (QTcF) must be used for clinical decisions. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

Clinically significant abnormalities present at screening should be reported on the appropriate CRF. New or worsened significant findings occurring after informed consent must be recorded as adverse events.

In case of QTcF prolongation, please refer to Section 6.6.5.2 "Follow up for QTcF prolongation"

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated and transmitted electronically to the central ECG vendor as unscheduled timepoints. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

Table 8-10 Central ECG collection plan in Part 1

Cycle	Day	Time point*	Number of ECG Replicates
Screening	Day -28 to Day -1	anytime	12 Lead Triplicate
CONF Cycle 1	Day 1	Pre-dose[1] Post-dose 3h[2] Post-dose 8h[2]	12 Lead Triplicate
	Day 5	Pre-dose[1] Post-dose[2] 3h Post-dose[2] 8h	12 Lead Triplicate
CONF Cycle 4	Day 1	Pre-dose[1]	12 Lead Triplicate
		Post-dose[2] 3h	12 Lead Triplicate
EOT		Anytime	12 Lead triplicate
Unscheduled or Unplanned sample		Anytime as clinically indicated	12 Lead triplicate

* When PK is collected at the same time point as ECG, the PK sample should be taken immediately after ECG
[1]ECG collection prior to any study drug dosing
[2] ECG collection after siremadlin intake

Table 8-11 Central ECG collection plan in Part 2

Cycle	Day	Time point*	Number of ECG Replicates
Screening	Day -28 to Day -1	anytime	12 Lead Triplicate
PRIM Cycle 1	Day 1	Pre-dose[1] Post-dose 3h[2] Post-dose 8h[2]	12 Lead Triplicate

	Day 5	Pre-dose[1] Post-dose[2] 3h Post-dose[2] 8h	12 Lead Triplicate
PRIM Cycle 4 - If participant entered combination prior to reaching cycle 4 in priming, perform ECG assessment at COMB Cycle 1 as indicated below	Day 1	Pre-dose[1] Post-dose[2] 3h	12 Lead Triplicate 12 Lead Triplicate
COMB Cycle 1 - To be performed only if participant entered combination prior to completion of cycle 4 in Priming	Day 1	Pre-dose[1] Post-dose[2] 3h	12 Lead Triplicate 12 Lead Triplicate
EOT	N/A	Anytime	12 Lead Triplicate
Unscheduled or Unplanned sample		Anytime as clinically indicated	12 Lead Triplicate

* When PK is collected at the same time point as ECG, the PK sample should be taken immediately after ECG
[1] ECG collection prior to any study drug dosing
[2] ECG collection after siremadlin intake

8.4.2.1 Cardiac imaging - MRA (magnetic resonance angiography), MUGA (multiple gated acquisition) scan or echocardiogram

The left ventricular cardiac function will be evaluated by echocardiogram or MUGA at baseline according to the visit schedule in Table 8-1; Table 8-2; Table 8-3; and Table 8-4 and if clinically indicated.

8.4.2.2 Cardiac enzymes

Not applicable

8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner during the study until 2 weeks after the last dose of siremadlin. In addition, male participants should not donate sperm for the time period specified above.

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

At screening, a serum pregnancy test (serum ß-HCG) must be performed within 72 hours before the first dose.

During the study, a urine/serum pregnancy test should be performed at Day 1 of each cycle (except Cycle 1 if a pregnancy test had been performed within 72 hours of the first dose) and a serum pregnancy test at EOT visit. Pregnancy testing (urine/serum) should occur at Day 30 of the safety follow-up period. Refer to Table 8-1; Table 8-2; Table 8-3; and Table 8-4 for pregnancy testing schedule.

Positive urine pregnancy needs to be confirmed with a serum test. Confirmed positive pregnancy test requires immediate discontinuation of study treatment and discontinuation from study. See Section 10.1.4 for pregnancy reporting.

The pregnancy tests will be recorded only in the source documentation, not in the CRF.

Women of childbearing potential should employ the use of highly effective contraception during the study until 2 weeks after the last dose of siremadlin. Highly effective contraception methods are defined in Section 5.2.

As per Section 4.6, during a public health emergency as declared by local or regional authorities' i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of fertility

A woman is considered of childbearing potential from menarche and until becoming post menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.4 Other safety evaluations

8.4.4.1 aGvHD assessment

aGvHD staging and grading will be performed by the Investigator at baseline, at Day 1 visit of treatment cycles as outlined in the various treatment phases (Part 1 and Part 2)), at EOT visit, at the Safety Follow-up visit, every 3 months during post treatment Follow-up, and as clinically indicated as outlined in Table 8-1, Table 8-2, and Table 8-3, and Table 8-4.

aGvHD grading and staging will be performed using standard criteria (Harris et al 2016): measures of body surface area aGvHD skin rash, stool volumes or frequency per 24h time period, and serum bilirubin levels, staging by organ (skin; liver; upper GI; lower GI) and overall grading at the time of the evaluation should be reported according to Appendix 1 Section 16.1.

The data should be entered in the appropriate CRFs.

In addition, Investigator should record and report any management action of aGvHD in appropriate CRF(s).

Note: Additional aGvHD assessments (including biopsy of the organ involved) may be done as per institutional guidelines at investigator’s discretion. aGvHD assessments performed at unscheduled visit and leading to a change in patient's management after the last dose of study treatment should be recorded in the CRF.

8.4.4.2 cGvHD assessment

Occurrence of definitive and possible manifestations of cGvHD will be assessed by the Investigator at baseline, at Day 1 visit of treatment cycles as outlined in the various treatment phases (Part 1 and Part 2), at EOT visit, at the Safety Follow-up visit, every 3 months during post treatment Follow-up, and as clinically indicated as outlined in Table 8-1, Table 8-2, Table 8-3 and Table 8-4.

Occurrence of cGvHD will be reported on appropriate specific CRF.

Investigator will assess cGvHD as per NIH consensus guidelines for cGvHD (Appendix 2, Section 16.2): overall grading (mild, moderate, severe) at the time of cGvHD diagnosis which will be reported in corresponding CRF.

Additional cGvHD assessments (including biopsy of the organ involved) may be done as per institutional guidelines at investigator's discretion.

In addition, Investigator should indicate if a systemic treatment is initiated for cGvHD in appropriate CRF(s).

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population, including acute and chronic GvHD as potential complication of allo-SCT and DLI.

8.5 Additional assessments

8.5.1 Pharmacokinetics

Pharmacokinetic (PK) samples will be obtained and evaluated in all participants at all siremadlin dose levels. The exact dates and clock times of study drugs administration and sample blood collection will be recorded on the appropriate CRF. Any sampling issues should be noted on the CRF and on appropriate source documentation.

If participants experience an SAE or an AE leading to the discontinuation of the study treatment, an unscheduled PK blood sample should be obtained as close as possible to the event occurrence. The date and time of the last dose and the time of PK blood draw should be recorded.

[redacted]

8.5.1.1 Pharmacokinetic blood collection and handling

- All sampling is relative to the administration of siremadlin.
- Serial blood samples from all enrolled participants will be collected at specified time points as outlined in Table 8-12 and Table 8-13 to measure siremadlin PK.
- On days of sample blood collection, participants should take their medication at the clinic immediately after the first blood sample (e.g., pre-dose/0 hr sample). The exact dates and clock times of study drugs administration and sample blood collection will be recorded on

the appropriate CRF. Any sampling issues should be noted on the CRF and on appropriate source documentation.

- Blood samples of 2 mL per time point will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein opposite to the arm used for infusion (when applicable).
- When PK is collected at the same time point as ECG, the PK sample should be taken immediately after ECG.
- If vomiting occurs within 4 hours following siremadlin administration on the day of a post dose PK blood sample collection, the clock time of vomiting should be recorded in the appropriate CRF page.
- After permanent discontinuation of siremadlin, the samples scheduled for pre- and post-siremadlin treatment (Table 8-12 and Table 8-13) should no longer be collected.

Refer to the [CHDM201K12201 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

Table 8-12 Pharmacokinetic blood collection log for siremadlin (Part 1)

Cycle	Day	Scheduled Time Point (sampling window)
Dose Confirmation (CONF)		
CONF Cycle 1	1	Pre-dose/0 h [a, c]
		0.5 h (±10 min)
		1 h (±10 min)
		2 h (±10 min)
		3 h (±15 min) [c]
		6 h (±15 min)
		8 h (±30 min) [c]
		10 (±30 min)
		24h (±2h)
	5	Pre-dose/0 h [c]
		0.5 h (±10 min)
		1 h (±10 min)
		2 h (±10 min)
		3 h (±15 min) [c]
		6 h (±15 min)
		8 h (±30 min) [c]
CONF Cycle 5	1	Pre-dose/0 h [a]
		0.5 h (±10 min)
		1 h (±10 min)
		2 h (±10 min)
		3 h (±15 min)
		6 h (±15 min)
		8 h (±30 min)
	5	Pre-dose/0 h
		0.5 h (±10 min)
		1 h (±10 min)

Cycle	Day	Scheduled Time Point (sampling window)
		2 h (±10 min)
		3 h (±15 min)
		6 h (±15 min)
		8 h (±30 min)
CONF Cycles 4, 7, 10, 13, and 19	1	Pre-dose/0 h a
		3 h (±15 min)
Unscheduled sample	-	Unscheduled Anytime [b, c]

[a] Collect PK sample immediately prior to siremadlin administration
[b] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely identified.
[c] When PK is collected at the same time point as ECG, the PK sample should be taken immediately after ECG.

Table 8-13 Pharmacokinetic blood collection log for siremadlin (Part 2)

Cycle	Day	Scheduled Time Point (sampling window)
PRIMING (PRIM)		
PRIM Cycle 1	1	Pre-dose/0 h a, c
		0.5 h (±10 min)
		1 h (±10 min)
		2 h (±10 min)
		3 h (±15 min) [c]
		6 h (±15 min)
		8 h (±30 min) [c]
		10 (±30 min)
		24h (±2h)
	5	Pre-dose/0 h [c]
		0.5 h (±10 min)
		1 h (±10 min)
		2 h (±10 min)
		3 h (±15 min) [c]
		6 h (±15 min)
		8 h (±30 min) [c]
PRIM Cycle 5 Applicable to participants who did not enter combination phase. For participants who proceed to siremadlin/DLI, follow the schedule for combination phase, then proceed to maintenance phase assessment schedule.	1	Pre-dose/0 h [a]
		0.5 h (±10 min)
		1 h (±10 min)
		2 h (±10 min)
		3 h (±15 min)
		6 h (±15 min)
		8 h (±30 min)
	5	Pre-dose/0 h
		0.5 h (±10 min)
		1 h (±10 min)
		2 h (±10 min)
		3 h (±15 min)
		6 h (±15 min)
		8 h (±30 min)

Cycle	Day	Scheduled Time Point (sampling window)
PRIM Cycles 4, 7, 10, 13, and 19	1	Pre-dose/0 h [a] 3 h (±15 min)
COMBINATION (COMB)		
COMB Cycle 1 and COMB Cycle 3	1	Pre-dose/0 h a,c 0.5 h (±10 min) 1 h (±10 min) 2 h (±10 min) 3 h (±15 min)c 6 h (±15 min) 8 h (±30 min)
	5	Pre-dose/0 h a,c 0.5 h (±10 min) 1 h (±10 min) 2 h (±10 min) 3 h (±15 min)[c] 6 h (±15 min) 8 h (±30 min)
MAINTENANCE (MAINT)		
MAINT Cycle 1 Applicable to participants who received the combination phase (siremadlin/DLI). Otherwise, for participants who did not receive the combination phase; follow the assessment schedule for priming phase.	1	Pre-dose/0 h a 0.5 h (±10 min) 1 h (±10 min) 2 h (±10 min) 3 h (±15 min) 6 h (±15 min) 8 h (±30 min)
	5	Pre-dose/0 h a 0.5 h (±10 min) 1 h (±10 min) 2 h (±10 min) 3 h (±15 min) 6 h (±15 min) 8 h (±30 min)
MAINT Cycles 4, 7, 10, 13, and 19	1	Pre-dose/0 h a 3 h (±15 min)
Unscheduled sample	-	Unscheduled Anytime [b, c]

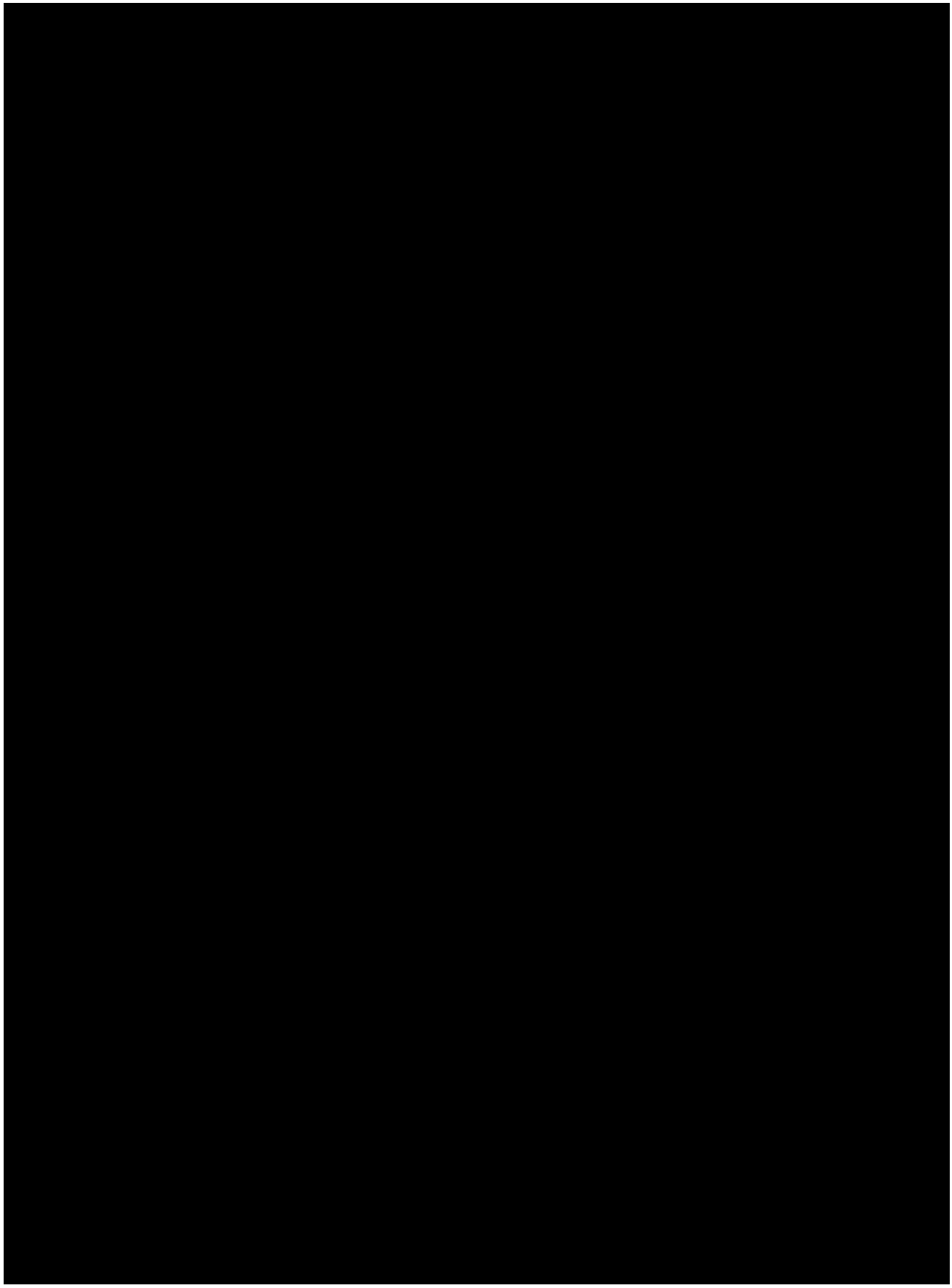
[a] Collect PK sample immediately prior to siremadlin administration
[b] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely identified
[c] When PK is collected at the same time point as ECG, the PK sample should be taken immediately after ECG

8.5.1.2 Analytical method

Plasma concentrations of siremadlin will be determined using a validated LC-MS assay, with a current lower limit of quantification (LLOQ) of 1 ng/mL. The details of the assay will be documented in the [CHDM201K12201 Laboratory Manual].

Concentrations will be expressed in mass per volume units. Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

[redacted]



9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when the treatments (siremadlin monotherapy or siremadlin in combination with DLI) is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the investigator. Discontinuation of DLI only while continuing siremadlin monotherapy is NOT considered a study treatment discontinuation.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations Section 6.2.3.
- Any situation in which continued study participation might result in a safety risk to the participant
- Any adverse event or laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study.
- Protocol defined reasons for discontinuation (see Section 6.1.4)
- Termination of the study by Novartis

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Section 8 and below).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

9.1.1.1 Safety Follow-up

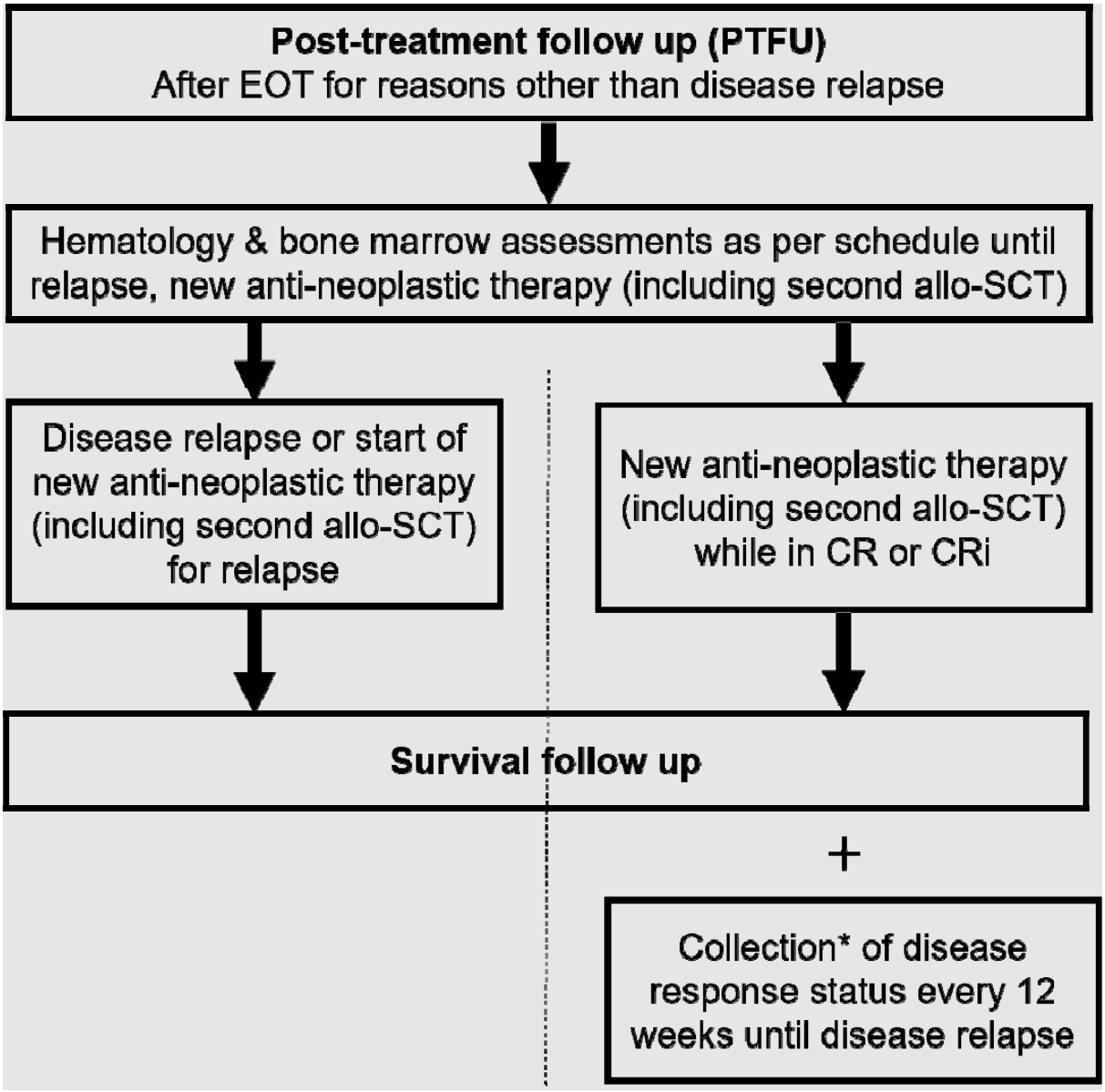
All participants who discontinue from study treatment must be followed for safety for 30 days after the last dose of siremadlin. All safety assessments should be completed as per Table 8-1 and Table 8-2. However, if the participant begins new anti-neoplastic therapy before the end of the safety follow-up period, the collection of new SAEs and AEs unrelated to study medication will stop, and thereafter only AEs and SAEs suspected to be related to study treatment will continue to be collected up to the end of the safety follow-up period. Suspected SAEs will continue to be collected beyond the 30-Day safety visit (in Post-Treatment follow-up). For female participants of childbearing potential, a pregnancy test will be performed at the timepoints listed in Table 8-1 and Table 8-2.

9.1.1.2 Post-Treatment Follow-up

For participants who completed the planned study treatment (24 cycles) or discontinued treatment earlier for reasons other than documented disease relapse, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, efficacy assessments will

continue to be performed as per Table 8-1 and Table 8-2 with hematological assessments and bone marrow assessments or as clinically indicated until documented disease relapse, start of a new anti-neoplastic treatment (including second allo-SCT), death, lost to follow-up, or withdrawal of consent/exercice of participants' data privacy rights.

Figure 9-1 Post Treatment and Survival Follow up Design



* Via phone call or on site visit if participant happens to be visiting the site

9.1.1.3 Survival Follow-up

Participants will enter the survival follow-up period once they complete the safety follow-up period or for those who had entered the post-treatment follow-up phase, once they have disease relapse or started a new anti-neoplastic therapy (including second allo-SCT) (whichever is

later). Participants will then be contacted by telephone every 12 weeks or if they happen to be visiting the site to follow-up on their survival status. Any new anti-neoplastic therapy that has been started since the last contact date (including second allo-SCT) and any SAEs related to study treatment will also be collected during these phone calls. Additionally, for participants who start a new anti-neoplastic therapy (including second allo-SCT) but remained in CR/CRi, disease response status per the investigator's local assessments (if available) will be collected every 12 weeks (if participant happens to be visiting the site) until documented disease relapse (Figure 9-1).

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/exercice of participants' data privacy rights, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent and exercise of participants' data privacy rights

Participants may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent/opposition to use of data and/ or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations(e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/ exercice data privacy rights and record this information. The Investigator shall clearly document if the participant has witdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/ exercice dataprivacy rights should be made as detailed in Section 8.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

Following completion of the safety follow-up period and/or post-treatment follow-up period, all participants will be followed for survival (see Section 9.1.1.3).

The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

The primary CR rate analysis will be conducted after the last participant enrolled and treated has completed 6 months from start of study treatment. Following the cut-off date for the analysis reported in the primary Clinical Study Report (CSR), the study will remain open and ongoing participants will continue to receive study treatment and be followed per the schedule of assessments until discontinuation criteria is met per Section 9.1.1.

The end of study (EOS) is defined as the earliest occurrence of one of the following:

- All participants have been followed for at least 3 years since start of study treatment or have died, been lost to follow-up or have withdrawn consent to further participation in the study.

At the end of the study, in alignment with local regulations, treatment continuity will be offered outside this study through an alternative setting to participants who are receiving treatment with siremadlin and in the opinion of investigator are still deriving clinical benefit. Safety will be monitored and reported to Health Authorities as per regulatory requirements.

The final analysis will occur at the end of the study. All available data from all participants up to this cut-off date will be analyzed and summarized in a final CSR.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development
- Practical reasons (including slow enrollment),
- Regulatory reasons
- Medical reasons

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible to perform their End of Treatment (EOT) Visit and the assessments for EOT as described in Section 8 and will be treated as a participant who discontinued from study treatment. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

In the event that the study is terminated prematurely, e.g., due investigator recommendation at the safety review meeting or Novartis decision, participants still receiving study treatment and who, according to investigator assessment, continue to benefit from the treatment, will be offered to continue study treatment as per protocol or through an alternative setting (see Section 9.3).

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered

by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The Common Toxicity Criteria (CTC) AE grade (CTCAE version 5.0 or higher) will be used for grading of all adverse events except for GvHD (Harris et al 2016 for aGvHD and NIH consensus criteria for cGvHD (Jagasia et al 2015)).
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported.
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding with study treatment.

   All adverse events must be treated appropriately. Treatment may include one or more of the following:

   - Dose not changed
   - Dose reduced/increased
   - Drug interrupted/permanently discontinued
6. Its outcome (i.e., recovery status or whether it was fatal).

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment OR until the start of a new antineoplastic medication if sooner than 30 days after last dose of the study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Disease progression (including fatal outcomes), if documented by use of appropriate method, should not be reported as a serious adverse event, except if the investigator considers that progression of malignancy is related to study treatment.

Adverse events separate from the progression of malignancy (for example deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity.
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
    - social reasons and respite care in the absence of any deterioration in the participant’s general condition.
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.

- is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the end of the safety follow-up period (Section 9.1.1) must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form in the eCRF; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAE reporting timeframes and conditions:

1. Treated participants: ALL SAEs that occurred between the time participant has provided informed consent until 30 days after the participant has discontinued or stopped study treatment must be reported to the Novartis Chief Medical Office and Patient Safety (CMO & PS) irrespective of the investigator's assessment of causality
2. Participants who are screened but have not received any study treatment: ALL SAEs that occurred after the participant has provided informed consent and through the time the participant is deemed a Screen Failure and/ or dropped-out the study due any reason without receiving the study medication must be reported to the Novartis CMO & PS irrespective of the investigator's assessment of causality
3. Any SAEs that occurred after the 30-day period past the last dose of study treatment should only be reported to the Novartis CMO & PS if the investigator suspects a causal relationship with the study treatment, unless otherwise specified by local law/regulations.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

For all pregnancies with live birth and/or unknown outcome the newborn has to be followed up to obtain infant health status and development up to twelve months after delivery.

10.1.5 Reporting of infection

Infections will be reported as adverse events and the AE severity grade will be assessed according to CTCAE grading as defined in Section 10.1.1 .

In addition, Investigators will detail the type of infection as well as the method of diagnosis and assess the event according to the Infection Severity grading (BMT CTN 2013, Section 16.3 Appendix 3).

10.1.6 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

Not applicable.

10.3 Committees

10.3.1 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial, i.e., not being Novartis representatives from the Clinical Trial Team (CTT).

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will periodically

review the study data and will make recommendations on the study conduct (including study termination). The SC will review protocol amendments as appropriate. Together with the CTT, the SC will also develop recommendations for publications of study results including authorship rules.

The details of the role of the steering committee will be defined in the Steering Committee charter.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the Electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

In addition to data entered into the eCRF, requisition forms may also need to be completed for (e.g., PK, [redacted] etc.) sample collection. After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated Contract Research Organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, enrollment, and screen failures, as well as data about study drugs dispensed to the participant globally will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. A central analytics organization may analyze data & identify risks & trends for site operational parameters and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The primary safety analysis for Part 1 will be performed after participants at each dose level in dose-determining set of Part 1 have completed DLT observation period of one cycle.

The primary safety analysis for Part 2 will be performed after each participant in dose-determining set of Part 2 has completed at least one cycle of siremadlin/DLI combination.

The primary efficacy analysis will be performed on all participant data at the time all participants will have completed at least 6 months or discontinued earlier.

The final efficacy and safety analysis will be performed at the end of study as defined in Section 9.3.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented when applicable.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all participants that received any study drug (i.e. at least one dose of siremadlin with or without DLI).

The Safety Set includes all participants from the FAS.

The Dose-Determining Set (DDS) includes all participants during the dose determination phase of the study (DLT assessment) who met the minimum required number of treatment cycles(s), met the minimum exposure criteria (MEC), met the minimum follow up/observation after treatment and have sufficient safety evaluations, or have experienced a DLT during the observation period.

There are two DDSs: DDS1 for Part 1 and DDS2 for Part 2:

- DDS1 (Part 1): consists of participants who met the MEC1 and had sufficient safety evaluations or had a DLT during Cycle 1. A participant has met the MEC1 if they have received during the first cycle at least 75% of the total planned doses for siremadlin (e.g., ≥ 4 out of 5 daily doses of siremadlin). Participants receiving a reduced dose of siremadlin due to co-administration of strong or moderate CYP3A4 inhibitors as described in Section 6.2.2.1, will be considered to have received the full planned dose. Participants who do not experience a DLT during Cycle 1 are considered to have sufficient safety evaluations if they have been observed at least from Day 1 to the end of Cycle 1 following the first dose of siremadlin, and are considered by both the sponsor and investigators to have enough safety data to conclude that a DLT did not occur.
- DDS2 (combination phase in Part 2): consists of participants who met the MEC2 for at least Cycle 1 of combination and had sufficient safety evaluations or had a DLT during combination phase. A participant has met the MEC2 if they have received the planned dose of DLI and at least 75% of the total planned doses for siremadlin as defined in the dose and treatment schedule (see Section 6.3.2) for a given cycle. Participants receiving a reduced dose of siremadlin due to co-administration of strong or moderate CYP3A4 inhibitors as described in Section 6.2.2.1, will be considered to have received the full planned dose. Participants who do not experience a DLT during cycle(s) of DLI administration (combination phase) are considered to have sufficient safety evaluations if they have been observed at least from Day 1 to the end of their combination phase,and are considered by both the sponsor and investigators to have enough safety data to conclude that a DLT did not occur. Participants will be analyzed according to the study treatment received as defined for FAS.

The Pharmacokinetic analysis set for all (PAS-all) includes all participants in the safety set who provide at least one evaluable PK concentration of siremadlin (see Section 8.5.1.1 and Section 12.5.3).

For a concentration to be evaluable:

- Dosing information must be properly documented (data and time of administration)
- Participant takes the dose of study treatments as described in Section 6.3.2
- Participant did not vomit within 4 hours after the oral dosing of siremadlin
- For pre-dose samples: the sample is collected before the next dose administration
- For post-dose samples: the planned dose of siremadlin must be taken prior to sampling

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for all participants for the FAS separately for Part 1 and Part 2.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term.

12.3 Treatments

The Safety set will be used for the analyses below.

Exposure to siremadlin in Part 1 will be summarized by dose cohort. In Part 2 the duration of exposure to siremadlin by priming phase, combination phase, maintenance phase, and entire treatment period, and to DLI as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

The number of participants with dose adjustments and the reasons will be summarized by study part, siremadlin and DLI. All dosing data will be listed

12.4 Analysis supporting primary objectives

The primary safety objective is to confirm the dose and schedule that are tolerable and safe without unacceptable toxicities (dose limiting toxicities [DLTs]) of siremadlin monotherapy in Part 1 and for siremadlin in combination with DLI in Part 2.

The primary efficacy objective is to evaluate the preliminary efficacy of siremadlin study treatment strategy (siremadlin monotherapy, as priming and/or maintenance, with or without siremadlin in combination with DLI) in Part 2, on prevention of hematologic relapse.

12.4.1 Definition of primary endpoint(s)

The primary safety endpoints are the incidence of DLTs in Part 1 and time-to-DLT in Part 2 respectively during DLT evaluation period for participants included in the DDS.

The primary efficacy endpoint of the study is the proportion of participants who are alive and remain in CR/Cri with no evidence of hematologic relapse over at least 6 months after the start

of study treatment (siremadlin monotherapy, as priming and/or maintenance, with or without siremadlin in combination with DLI in Part 2. (Cheson et al 2003, Döhner et al 2017 and Table 8-3).

12.4.2 Statistical model, hypothesis, and method of analysis

Primary safety analysis (incidence of DLT and time-to-DLT)

For participants in the Cycle 1 of Part 1 and the entire combination phase in Part 2, assessing whether siremadlin at the tested dose levels does not lead to an unacceptable level of toxicity (DLTs) when administered alone or in combination with DLI will be based on the estimation of the probability of DLT for participants in the DDS1 for Part 1 and of time to DLT for the participants in the DDS2 for combination phase in Part 2. Dose confirmation of siremadlin as monotherapy (Part 1) will be based on the incidence of DLTs and will be guided by a Bayesian logistic regression model with the EWOC principle that the risk of excessive toxicity (DLT rate ≥ 33%) is less than 25% (EWOC principle, Babb et al 1998). The starting dose level of the priming phase is 30 mg siremadlin QD (Day 1 to 5, 28-day cycle). Dose confirmation of siremadlin in combination with DLI (siremadlin/DLI combination phase in Part 2) will be based on time-to-DLT using Bayesian time to first DLT model with the EWOC principle considering all available information for up to 3 cycles. A full assessment of the prior risk to participants and a summary of the operating characteristics of the models is given in Section 16.6 and Section 16.7.

Primary efficacy analysis (proportion of participants who remain in CR/CRi 6 months after the start of study treatment)

The efficacy of study treatment will be based on the proportion of participants remaining in CR/CRi as per investigator assessment for at least 6 months after the start of study treatment among participants who initiated priming phase at the siremadlin RD for priming with/without DLI (Part 2). Assuming a minimally informative prior distribution (Beta(0.67,1) with mean 40% based on the null value (details on null value in Section 1) in the statistical criterion, the distribution of the CR/CRi rate will be updated with all available data from participants who are in the FAS and have initiated siremadlin (at RD for priming or a tolerated siremadlin dose lower than RD for priming) as monotherapy with or without siremadlin/DLI combination.

Decision criteria for trial success (dual-criterion) are based on proportion of participants who remain in CR/CRi by investigator assessment and are alive at least 6 months after the start of study treatment):

- Bayesian statistical significance: probability (CR/CRi rate > 40% | data) ≥ 0.975 (the one-sided p-value must be less than 2.5%) (null value), and
- Clinical relevance: posterior median of CR/CRi rate ≥ 60% (decision value)

The results will be also presented with a frequentist formulation. The CR/CRi rate and the exact 95% confidence interval (CI) (Clopper and Pearson 1934), as well as the 1-sided p-value will be provided. The test will be performed using an overall one-sided 2.5% level of significance. Thus, the null hypothesis (H_0:CR/CRi ≤ 40%) will be rejected if the lower bound of the two-sided 95% exact CI is >40%.

The analysis will be performed using data up to the analysis data cut-off date, which will be at the time all participants who are in FAS and initiated priming phase at RD for priming with/without DLI will have completed at least 6 months or discontinued earlier.

12.4.3 Handling of intercurrent events of primary estimand

Handling of intercurrent events of the primary efficacy and safety estimands is described in Section 2.1.

12.4.4 Handling of missing values not related to intercurrent event

For the determination of CR/CRi, an adequate response assessment is considered any disease assessment indicating response status apart from “unknown” or “not done”. If no subsequent assessment or the subsequent assessment of an inadequate response does not show CR/CRi, the inadequate response will be regarded as no CR/CRi.

12.4.5 Sensitivity analyses

Sensitivity analyses (if appropriate) will be described in the Statistical Analysis Plan (SAP).

12.4.6 Supplementary analysis

Supplementary analyses (if appropriate) will be described in the SAP.

12.5 Analysis supporting secondary objectives

The secondary objectives for Part 2 are to assess the effect of siremadlin with/without DLI on safety and tolerability, Relapse free survival (RFS), Cumulative incidence of relapse, Overall Survival (OS), proportion of participants stopping study treatment due to GvHD/AE, incidence of treatment-emergent GvHD, GvHD-free/relapse-free survival (GRFS), and PK. A separate objective for Part 1 siremadlin monotherapy is to evaluate the preliminary efficacy of siremadlin monotherapy on prevention of hematologic relapse at the recomended dose for Part 2.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Efficacy endpoints will be analyzed and summarized for the FAS and by dose level of siremadlin in priming phase unless otherwise specified.

Time-to-event endpoints will be analyzed using Kaplan-Meier method for participants in the FAS who initiated priming phase at siremadlin RD for priming: the Kaplan-Meier curves, medians and 95% CI of the medians will be presented.

No formal statistical tests will be performed for any of the secondary efficacy endpoints and hence no multiplicity adjustment will be applied.

Relapse-Free Survival (RFS)

RFS is defined as the time from start of study treatment to the date of first documented hematologic relapse or death due to any cause, whichever occurs first. RFS will be censored if no RFS event is observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-neoplastic therapy is started. The censoring date will be the date of

the last adequate response assessment. The handling of intercurrent events will be the same as the primary estimand (Section 2.1).

RFS will be analyzed in the FAS population who initiated priming phase at siremadlin RD for priming and the RFS distribution will be estimated using the Kaplan-Meier method. Kaplan-Meier curve, median and 95% confidence interval of the median will be presented. The KM estimates at 1 year and 2 year will be presented with their 95% CI.

Cumulative incidence of relapse

Cumulative incidence of relapse (CIR) is defined as the time from start of study treatment to the date of first documented hematologic relapse. Participants will be censored if no relapse is observed before the first to occure between: (i) the analysis cut-off date, and (ii) the date when a new anti-neoplastic therapy is started. The censoring date will be the date of the last adequate response assessment.

CIR will be analyzed in the FAS population who initiated priming phase at siremadlin RD in Part 2 and who are at the RD in Part 1 nd will be estimated using the Kaplan-Meier method. CIR curve will be presented as well as the CIR estimates at 1 year and 2 year with their 95% CI.

Overall Survival (OS)

OS is defined as the time from start date of treatment to date of death due to any cause. If a participant is not known to have died, then OS will be censored at the latest date the participant was known to be alive (on or before the cut-off date). All deaths will be taken into account whenever the death occurred, i.e. even after new anti-neoplastic therapy, allo-SCT, interruptions, or discontinuation of study treatment due to any reason. OS will be estimated by Kaplan-Meier method for participants who initiate priming phase at siremadlin RD for priming. The median OS and 95% CI will be presented.

GvHD-free/relapse-free survival (GRFS)

GRFS is defined as the time from start of treatment to the date of first documented occurrence or worsening of treatment emergent grade III or IV aGvHD or cGvHD requiring initiation of systemic immunosuppressive treatment, hematologic relapse, or death due to any cause, whichever occurs first. GRFS will be censored if no GRFS event is observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-neoplastic therapy is started. The censoring date will be the date of the last adequate response assessment of GvHD assessment given confirmed remission in a subsequent efficacy assessment.

GRFS will be analyzed in the FAS population and the GRFS distribution will be estimated using the Kaplan-Meier method. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented.

Participants remaining in CR/CRi (in Part 1)

The participants who are alive and maintained CR/CRi with no eveidence of hematologic relapse over at least 6 months after start of siremadlin monotherapy [Part 1 - siremadlin monotherapy at the recommended dose for Part 2].

12.5.2 Safety endpoints

Safety analyses will be summarized for the safety set and by dose level of siremadlin by treatment phase and study part.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The overall observation period will be divided into three mutually exclusive segments for the entire treatment period:

1. Pre-treatment period: from day of participant's informed consent to the day before first administration of siremadlin.
2. On-treatment period: from date of first administration of siremadlin 30 days after date of last administration of siremadlin if monotherapy is used in last cycle, or 42 days after date of last administration of siremadlin if combination with DLI therapy is used in last cycle.
3. Post-treatment period: any observation starting at Day 31 after last administration of siremadlin if monotherapy is used in last cycle, or at Day 43 after date of last administration of siremadlin if combination with DLI therapy is used in last cycle.

The on-treatment period is further divided by treatment phase(s) for Part 2:

Priming phase: from date of first administration of siremadlin to 30 days after date of last administration of siremadlin in priming phase, or until the first administration of siremadlin in combination phase.

Combination phase: from date of first administration of siremadlin in first combination with DLI cycle to 42 days after date of last administration of siremadlin in combination phase, or until the first administration of siremadlin in maintenance phase.

Maintenance phase: from date of first administration of siremadlin to 30 days after date of last administration of siremadlin in maintenance phase.

Adverse events

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period. The number (and percentage) of participants with treatment emergent adverse events will be summarized by primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

Separate summaries will be provided for:

- treatment emergent grade III or grade IV acute GvHD
- treatment emergent moderate to severe chronic GvHD

Serious adverse events and non-serious adverse events will be tabulated. All deaths (on-treatment and post-treatment) will be summarized.

In addition, all AEs and SAEs which started during the overall safety period will be summarized. All reported AEs will be listed and those that started during the pre-treatment, on-treatment period and post-treatment period will be flagged.

Vital signs

All vital signs abnormalities will be summarized.

12-lead ECG

HR and QTcF will be obtained from 12-lead ECGs for each participant at screening and during the study. ECG data will be read and interpreted centrally.

Categorical analysis of QTcF interval and HR data will be based on the summary of number of participants meeting or exceeding predefined limits.

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

For laboratory tests where grades are defined by CTCAE v5.0:

- Shift tables using CTCAE v5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v5.0:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value

ECOG PS

ECOG PS will be summarized at each time point during the study.

12.5.3 Pharmacokinetics

Siremadlin drug concentrations

Pharmacokinetic parameters will be derived from the individual concentration versus time profile using a non-compartmental method as implemented in Phoenix WinNonlin (Version 8.0 or higher; Pharsight, Mountain View, CA). The pharmacokinetic parameters described in Table 12-1 will be determined as deemed appropriate. Additional PK parameters may be estimated as needed. Pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin.

Table 12-1 Non-compartmental pharmacokinetic parameters*

AUC0-t	The area under the concentration vs. time Curve (AUC) from time zero to specified time point.Note: as the last sampling time of the PK profiles at PRIM Cycle 1 Day 1 is 24h postdose, AUC0-24h will be determined (when feasible) for siremadlin; for the PK profiles collected at Day 1 and Day 5 of other cycles, AUC0-8h will be determined (when feasible) for siremadlin
AUClast	The AUC from time zero to the last quantifiable concentration point (Tlast) (mass x time x volume^{-1})
Ctrough	Concentration that is just prior to the beginning of, or at the end, of a dosing interval; corresponding to the pre-dose concentration (when feasible)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration following drug administration (mass x volume^{-1})
C3h	Concentration at 3 hours post-dose (when feasible)
Tlast	Time at which the last measurable concentration was observed (time) Note: for the PK profiles of selected cycles
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after drug administration (time)

* Details of sampling time are included in Table 8-12 and Table 8-13.

The respective PAS for siremadlin will be used in all pharmacokinetic data analyses.

Siremadlin concentration data will be listed by participant, treatment phase, and visit/sampling time point (See Section 8.5.1 for details). Descriptive summary statistics for siremadlin concentrations will be provided by visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV) (arithmetic and geometric), median, minimum, and maximum, as well as the frequency (n, %) of concentrations below the lower limit of quantification (LLOQ) and reported as zero. Values below the LLOQ will be treated as missing for the calculation of the geometric means and geometric CV%.

The PAS will be used for the PK data analysis and PK summary statistics. Descriptive statistics of all pharmacokinetic parameters (e.g. AUCs, Cmax) will include arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing.

All concentration vs. time profiles data for siremadlin will be displayed graphically.

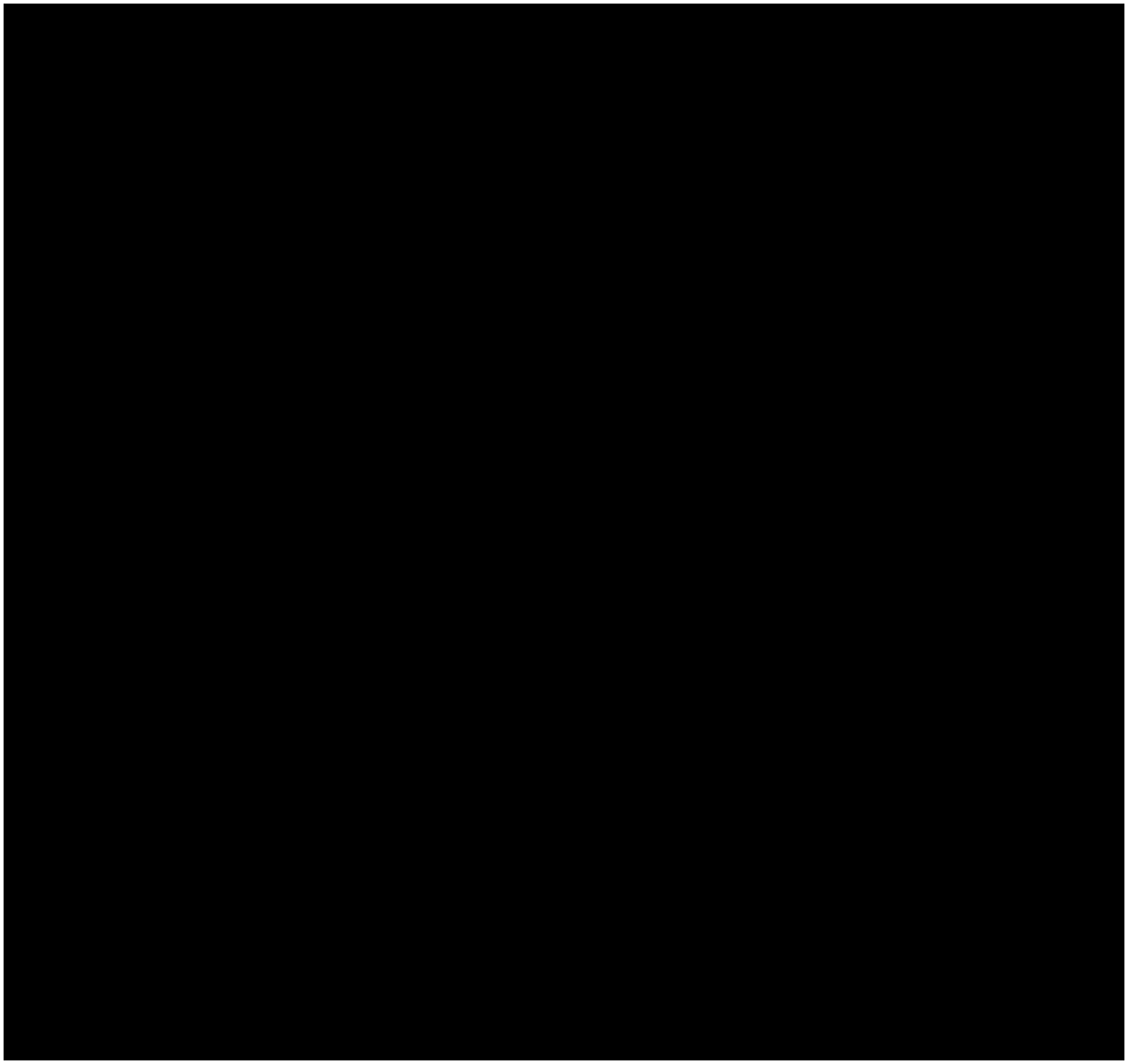
Population pharmacokinetic analysis (Siremadlin)

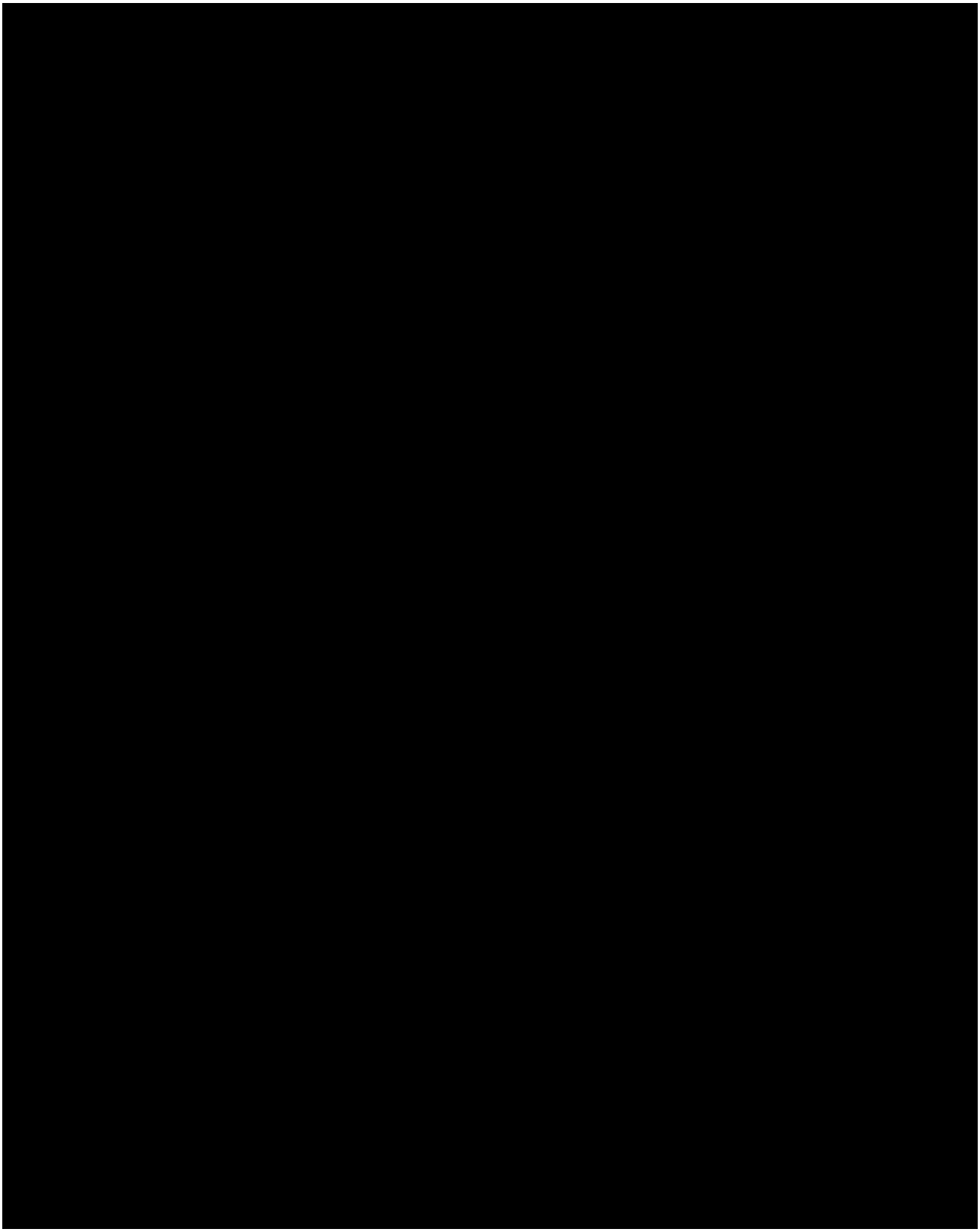
If there is sufficient data for analysis, the details of the population pharmacokinetic analyses may be provided in a separate reporting and analysis plan, and the results may be reported in a separate population pharmacokinetic report.

Drug concentrations of IST agents (tacrolimus, cyclosporine, sirolimus)

Blood concentration data of tacrolimus, cyclosporine, sirolimus collected by the investigator/per local institutional standard of practice will be listed by participant, and visit/sampling time point. Descriptive summary statistics for concentrations will be provided by visit/sampling time point.

All concentration vs. time data will be displayed graphically





12.7 Interim analyses

No formal interim analysis is planned for this trial.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Primary safety endpoint

No formal statistical power calculations to determine sample size were performed for this study.

For Part 1, initially, 3-6 participants will be enrolled at the starting dose level (siremadlin 30 mg QD D1-5) to have at least 3 evaluable participants. Upon observation of specific toxicities (see Section 6.6 for details), the participating Investigators and Novartis study personnel will decide to increase/decrease the dose or expand at 30 mg QD siremadlin. For a dose level to be considered for RD for Part 2, at least 6 evaluable participants are required. For combination phase in Part 2, the maximum RD for siremadlin/DLI combination will be decided with data from all evaluable participants (at least 9 evaluable participants are required) when they have completed siremadlin/DLI combination phase or experienced a DLT. For a dose level to be declared as maximum RD for combination it must be tested with at least 3 evaluable participants treated at or above that dose level.

Primary efficacy endpoint

The efficacy of study treatment will be based on the proportion of participants remaining in CR/CRi as per investigator assessment in Part 2. Decision criteria for trial success (dual criterion) are based on proportion of participants who remain in CR/CRi by investigator assessment and are alive at least 6 months after the start of study treatment):

- Bayesian statistical significance: probability (CR/CRi rate > 40% | data) ≥ 0.975 (the one-sided p-value must be less than 2.5%) (null value; details about rationale in Section 1), and
- Clinical relevance: posterior median of CR/CRi rate ≥ 60% (decision value)

With two criteria stated above the minimally required sample size (n_{min}) is 22, and the final sample size was set to 26 including participants who initiated priming phase at siremadlin RD for priming. For 26 participants (included for the primary efficacy analysis), the table below

shows data scenarios (number of participants remaining in CR/CRi) with respective inferential results and decisions.

Based on simulations (Table 12-2), a total of 16 responders out of 26 participants (62%) is required for trial success, with estimates of 60% for the posterior median CR/CRi rate and 98% for the posterior probability for a positive effect (CR/CRi >40%). If the number of participants with CR/CRi is less than 16, both criteria are not met (NO-GO).

Table 12-2 Data scenarios, inferential results and decisions (n=26)

Observed CR/CRi rate	Posterior median CR/CRi	Posterior probability for a positive effect (CR/CRi >40%)	Decision for trial success
10/26 (0.38)	0.38	0.43	Failed
11/26 (0.42)	0.42	0.58	Failed
12/26 (0.46)	0.46	0.73	Failed
13/26 (0.5)	0.49	0.84	Failed
14/26 (0.54)	0.53	0.92	Failed
15/26 (0.58)	0.57	0.96	Failed
16/26 (0.62)	0.6	0.98	Successful
17/26 (0.65)	0.64	0.99	Successful

A minimally informative prior distribution (Beta (0.67,1)) with mean 40% based on the null value in the statistical criteria has been used in these calculations. Operating characteristics for various true CR/CRi rates are presented in Table 12-3 below. The type-I error under the null value (CR/CRi rate = 40%) is 2% and power is 52% assuming a true CR/CRi rate of 60%.

Table 12-3 Operating characteristics for true CR/CRi rate (n=26)

True proportion of participants in CR/CRi	Probability of success (Go)	Probability of futility (No Go)
0.30	0.00	1.00
0.35	0.01	0.99
0.40*	0.02	0.98
0.45	0.07	0.93
0.50	0.16	0.84
0.55	0.32	0.68
0.60**	0.52	0.48
0.65	0.72	0.28
0.70	0.88	0.12
0.75	0.96	0.04
0.80	0.99	0.01

For a true CR/CRi rate of 40% (null value), the probability for a trial success is 2% (*type-I error)*. **For a true CR/CRi rate of 60%, the probability for a trial success is 52% (*power*). These calculations were made using the software R (version 3.6.1) using the RBestT package.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.

- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, [IDFU] Investigational directions for use, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs and regulatory authorities as required.
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with there requirements, policies, and procedures EC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority.

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement

to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g. Clinicaltrials.gov, EudraCT etc).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

13.4 Quality Control and Quality Assurance

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You Letter
- Plain language trial summary - after CSR publication
- Individual study results - after CSR publication

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Acute GvHD Staging Criteria (Harris et al 2016)

Organ staging will be performed according to updated NIH criteria as described by (Harris et al 2016) in Table 16-1.

Table 16-1 Acute GvHD Staging Criteria

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (stool output/day)
Stage 0	No active (Erythematous) GvHD rash	< 2mg/dL	No or intermittent nausea, vomiting or anorexia	Adult: < 500mL/day or < 3 episodes/day Child: < 10mL/kg/day or < 4 episodes/day
Stage 1	Maculopapular rash < 25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexia	Adult: 500-999mL/day or 3-4 episodes/dayChild: 10-19.9mL/kg/day or 4-6 episodes/day
Stage 2	Maculopapular rash < 25%-50% BSA	3.1-6 mg/dL		Adult: 1000-1500mL/day or 5-7 episodes/dayChild: 20-30mL/kg/day or 7-10 episodes/day
Stage 3	Maculopapular rash > 50% BSA	6.1-15mg/dL		Adult: > 1500mL/day or > 7 episodes/dayChild: > 30mL/kg/day or > 10 episodes/day
Stage 4	Generalized erythroderma (> 50% BSA) plus bullous formation and desquamation > 5%BSA	> 15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

Overall clinical grade (based on most severe target organ involvement):
Grade 0: No Stage 1-4 of any organ.
Grade I: Stage 1-2 skin without liver, upper GI or lower GI involvement.
Grade II: Stage 3 rash and/or stage 1 liver and/or Stage 1 upper GI and/or Stage 1 lower GI.
Grade III: Stage 2-3 liver and/or Stage 2-3 lower GI with Stage 0-3 skin and/or Stage 0-1 upper GI.
Grade IV: Stage 4 skin, liver or lower GI involvement, with Stage 0-1 upper GI

16.2 Appendix 2: Grading of Chronic GvHD (NIH Consensus Criteria)

Grading of chronic GvHD as described by (Jagasia et al 2015) should be performed as described below.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Organ scoring of chronic GvHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is

impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. To be completed by specialist or trained medical providers. **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: % FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms___	☐ Others (specify):

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Photographic Range of Motion (P-ROM)

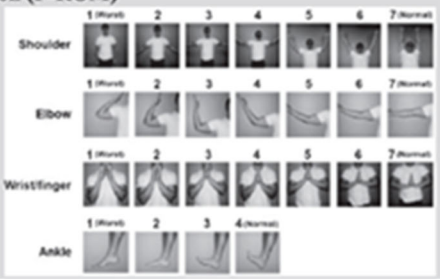

Table 16-2 NIH global severity of chronic GvHD

Mild	1 or 2 organs involved with no more than score 1 plus Lung score 0 ● Mild oral symptoms, no decrease in oral intake ● Mild dry eyes, lubricant eyedrops ≤ 3x/day
Moderate	3 or more organs involved with no more than score 1 OR Lung score 1 (FEV1 60-79% or dyspnea with stairs) OR At least 1 organ (not lung) or site with score 2 ● 19-50% body surface area involved or superficial sclerosis ● Moderate dry eyes, eyedrops ≥ 3x/days or punctal plugs
Severe	At least 1 organ or site with score 3 ● ≥ 50% body surface area involved ● Deep sclerosis, impaired mobility or ulceration ● Severe oral symptoms with major limitation in oral intake

	● Severe dry eyes affecting ADL OR Lung score 2 or 3(FEV1 40-59% or dyspnea walking on flat ground)
(Jagasia et al 2015, Lee 2017) Key points: In skin: higher of the 2 scores to be used for calculating global severity. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GvHD documented cause, that organ is not included for calculation of the global severity. If the abnormality in an organ is attributed to multifactorial causes (GvHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).	

16.3 Appendix 3: Infection Severity Grading

Infections will be categorized according to type (i.e. bacterial, viral and fungal) and Blood and Marrow Transplant Clinical Trials Network (BMT CTN) severity (i.e. grade III infection, yes vs. no) (BMT CTN 2013).

Table 16-3 Severity grading table and recurrence interval definitions

Type of Infection/ Severity grade	Grade 1	Grade 2	Grade 3
Bacterial infections	Bacterial focus NOS requiring no more than 14 days of therapy for treatment (e.g. urinary tract infection)	Bacteremia (except CoNS) without severe sepsis ***	Bacteremia with deep organ involvement (e.g. with new or worsening pulmonary infiltrates; endocarditis)
	Coag Neg Staph (S. epi), Corynebacterium, or Propioniobacterium bacteremia	Bacterial focus with persistent signs, symptoms or persistent positive cultures requiring greater than 14 days of therapy	Severe sepsis with bacteremia
	Cellulitis responding to initial therapy within 14 days	Cellulitis requiring a change in therapy d/t progression	Fasciitis requiring debridement
		Localized or diffuse infections requiring incision with or without drain placement	
		Any pneumonia documented or presumed to be bacterial	Pneumonia requiring intubation
			Brain abscess or meningitis without bacteremia
	C. Difficile toxin positive stool with diarrhea < 1L without abdominal pain (child < 20 mL/kg)	C. Difficile toxin positive stool with diarrhea > 1L (child > 20 mL/kg) or with abdominal pain	C. Difficile toxin positive stool with toxic dilatation or renal insufficiency with/without diarrhea
Fungal infections	Superficial candida infection (e.g. oral thrush, vaginal candidiasis)	Candida esophagitis (biopsy proven)	Fungemia including Candidemia
		Proven or probable fungal sinusitis confirmed radiologically without orbital, brain, or bone involvement	Proven or probable invasive fungal infections (e.g. Aspergillus, Mucor, Fusarium, Scedosporium)
			Disseminated infections (defined as multifocal pneumonia, presence of urinary or blood antigen, and/or CNS involvement) with Histoplasmosis, Blastomycosis, Coccidiomycosis, or Cryptococcus

Type of Infection/ Severity grade	Grade 1	Grade 2	Grade 3
			Pneumocystis jiroveci pneumonia (regardless of PaO2 level)
Viral Infections	Mucous HSV infection		
	Dermatomal Zoster	VZV infection with 3 or more dermatomes	Severe ZVZ infection (coagulopathy or organ involvement)
	Asymptomatic CMV viremia untreated or a CMV viremia with viral load decline by at least 2/3 of the baseline value after 2 weeks of therapy	Clinically active CMV infection (e.g. symptoms, cytopenias) or CMV viremia not decreasing by at least 2/3 of the baseline value after 2 weeks of therapy	CMV end-organ involvement (pneumonitis, enteritis, retinitis)
	EBV reactivation not treated with rituximab	EBV reactivation requiring institution of therapy with rituximab	EBV PTLD
	Adenoviral conjunctivitis asymptomatic viruria, asymptomatic stool shedding and viremia not requiring treatment	Adenoviral upper respiratory infection, viremia, or symptomatic viruria requiring treatment	Adenovirus with end-organ involvement (except conjunctivitis and upper respiratory tract)
	Asymptomatic HHV-6 viremia untreated or an HHV-6 viremia with a viral load decline by at least 0.5 log after 2 weeks of therapy	Clinically active HHV-6 infection (e.g. symptoms, cytopenias) or HHV-6 viremia without viral load decline 0.5 log after 2 weeks of therapy	
	BK viremia or viruria with cystitis not requiring intervention	BK viremia or viruria with clinical consequence requiring prolonged therapy and/or surgical intervention	
		Enterocolitis with enteric viruses	
		Symptomatic upper tract respiratory virus	Lower tract respiratory viruses
	Viremia (virus not otherwise specified) not requiring therapy	Any viremia (virus not otherwise specified) requiring therapy	
			Any viral encephalitis or meningitis
Parasitic infections			CNS or other organ toxoplasmosis
			Strongyloides hyperinfection
Nonmicrobiologically defined infections	Uncomplicated fever with negative cultures responding within 14 days		
	Clinically documented infection not requiring inpatient management	Pneumonia or bronchopneumonia not requiring mechanical ventilation	Any acute pneumonia requiring mechanical ventilation

Type of Infection/ Severity grade	Grade 1	Grade 2	Grade 3
		Typhlitis	
			Severe sepsis*** without an identified organism

*Concomitant or multimicrobial infections are graded according to the grade of the infection with the higher grade of severity.
**Therapy includes both PO and IV formulations.
***Severe sepsis definition (adults):
● Hypotension: A systolic blood pressure of <90 mmhg="" or="" a="" reduction="" of="">40 mmhg from baseline in the absence of other causes for hypotension
● Multiple Organ Dysfunction Syndrome: 2 or more of the following
  ● Renal failure requiring dialysis
  ● Respiratory failure requiring BiPAP or intubation
  ● Heart failure requiring pressors
  ● Liver failure

Disseminated Infections:
● Two or more non-contiguous sites with the SAME organism
● A disseminated infection can occur at any level of severity, but most will be grade 2 or 3.

Recurrence intervals to determine whether an infection is the same or new:
1. CMV, HSV, EBV, HHV6: 2 months (< 60 days)
2. VZV, HZV: 2 weeks (< 14 days)
3. Bacterial, non-C. difficile: 1 week (< 7 days)
4. Bacterial, C. difficile: 1 month (< 30 days)
5. Yeast: 2 weeks (< 14 days)
6. Molds: 3 months (< 90 days)
7. Helicobacter: 1 year (< 365 days)
8. Adenovirus, Enterovirus, Influenza, RSV, Parainfluenza, Rhinovirus: 2 weeks (< 14 days)
9. Polyomavirus (BK virus): 2 months (< 60 days)

For infections coded as “Disseminated” per the Infection Form, any previous infection with the same organism but different site within the recurrence interval for that organism will be counted as part of the disseminated infection.

16.4 Appendix 4: Prohibited medications and Concomitant medications to be used with caution and/or requiring actions during study drug treatment

In general, the use of any concomitant medication deemed necessary for the care of the participants is permitted in this trial, except as specifically prohibited in Section 6.2.2 and in Table 16-4 below. Refer to Section 6.2.2 for detailed guidance on restrictions. Some concomitant therapy to be used with caution or requiring action are described in Section 6.2.2.1 and in Table 16-5 below.

The list is adapted from the Novartis PK Sciences internal memorandum (2021): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies".

These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions.

If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

Table 16-4 List of prohibited medications during study treatment

Mechanism of Interaction	Drug Names
Narrow therapeutic index substrates of CYP3A	abemaciclib, acalabrutinib, alectinib, amiodarone, amitriptyline, astemizole, axitinib, baricitinib, bosutinib, brigatinib, cabazitaxel, cabozantinib, carbamazepine, ceritinib, clomipramine, cobimetinib, conivaptan, copanlisib, crizotinib, dabrafenib, dasatinib, dihydroergotamine, docetaxel, dronedarone, entrectinib, erdafitinib, ergotamine, everolimus, imipramine, ivosidenib, ixazomib, lomitapide, midostaurin, neratinib, nilotinib, panobinostat, pexidartinib, pimozide, ponatinib, quinidine, regorafenib, romidepsin, sonidegib, sorafenib, sunitinib, tamoxifen, temsirolimus, tolvaptan, trabectedin, vinblastine, zanubrutinib
Strong inducers of CYP3A	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John's wort (*Hypericum perforatum*)[1], avasimibe, rifapentine, apalutamide, ivosidenib
Moderate inducers of CYP3A	asunaprevir / beclabuvir / daclatasvir, bosentan, cenobamate, dabrafenib, elagolix, efavirenz, etravirine, lesinurad, lersivirine, lopinavir, nafcillin, phenobarbital, primidone, rifabutin, talviraline, telotristat ethyl, thioridazine, tipranavir/ritonavir[2]

[1] Herbal product
[2]Combination therapy

Table 16-5 List of medications to be used with caution and/or requiring actions during study treatment

Narrow therapeutic index substrates of CYP3A	cyclosporine, sirolimus, tacrolimus
Strong inhibitors of CYP3A	boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir[2] elvitegravir/ritonavir[2], grapefruit juice[1], idelalisib, indinavir, indinavir/ritonavir[2] itraconazole, josamycin, ketoconazole, lopinavir/ritonavir[2], mibefradil, mifepristone, nefazodone, nelfinavir, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[2], posaconazole, ribociclib, ritonavir, saquinavir,

	saquinavir/ritonavir[2], telaprevir, telithromycin, troleandomycin, tucatinib, voriconazole
Moderate inhibitors of CYP3A	aprepitant, amprenavir, atazanavir, atazanavir/ritonavir[2], casopitant, cimetidine, ciprofloxacin, darunavir, darunavir/ritonavir[2], diltiazem, duvelisib, erythromycin, faldaprevir, fedratinib, fluconazole, grapefruit juice[1], imatinib, isavuconazole, istradefylline, lefamulin, letermovir, Magnolia vine (*Schisandra sphenanthera*)[3], netupitant, ravuconazole, tofisopam, verapamil, voxelotor

[1] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent.
[2]Combination therapy
[3] Herbal product

16.5 Appendix 5: Patient Past History and Disease Characteristics

AML diagnosis: diagnosis of AML will be reported as defined by the 2016 World Health Organization (WHO) AML classification (Arber et al 2016).

Table 16-6 2016 WHO AML classification

1	AML with recurrent genetic abnormalities	● AML with t(8;21)(q22;q22), RUNX1-RUNX1T1. ● AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22), CBFB-MYH11. ● Acute promyelocytic leukemia (APL) with PML-RARA. ● AML with t(9;11)(p21.3;q23.3), MLLT3-KMT2A. ● AML with t(6;9)(p23;q34.1), DEK-NUP214. ● AML with inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2), GATA2, MECOM. ● AML (megakaryoblastic) with t(1;22)(p13.3;q13.3), RBM15-MKL1. ● AML with BCR-ABL1 (provisional entity). ● AML with mutated NPM1. ● AML with biallelic mutations of CEBPA. ● AML with mutated RUNX1 (provisional entity).
2	AML with myelodysplasia-related features	
3	Therapy-related myeloid neoplasms	
4	AML, Not Otherwise Specified (NOS)	● AML with minimal differentiation (FAB classification M0). ● AML without maturation (FAB classification M1). ● AML with maturation (FAB classification M2). ● Acute myelomonocytic leukemia (FAB classification M4). ● Acute monoblastic/monocytic leukemia (FAB classification M5a and M5b). ● Pure erythroid leukemia (FAB classification M6a and M6b). ● Acute megakaryoblastic leukemia (FAB classification M7). ● Acute basophilic leukemia. ● Acute panmyelosis with myelofibrosis.
5	Myeloid sarcoma	
6	Myeloid proliferations related to Down syndrome:	● Transient abnormal myelopoiesis (TAM). ● Myeloid leukemia associated with Down syndrome.
7	Acute Leukemias of Ambiguous Lineage	● Acute undifferentiated leukemia. ● Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); BCR-ABL1. ● MPAL with t(v;11q23.3); KMT2A rearranged. ● MPAL, B/myeloid, NOS. ● MPAL, T/myeloid, NOS.

Cytogenetics and risk stratification: cytogenetic risk category will be reported according to the 2017 European LeukemiaNet (ELN) recommendations (Döhner et al 2017).

Table 16-7 2017 ELN risk stratification by genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}† Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)

Risk category*	Genetic abnormality
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse

Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated RUNX1{
	Mutated ASXL1{
	Mutated TP53#

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.
*Prognostic impact of a marker is treatment-dependent and may change with new therapies.
†Low, low allelic ratio (,0.5); high, high allelic ratio ($0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and participants should not routinely be assigned to allogeneic HCT.
‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
§Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.
‖Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).
{ These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
#TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

Molecular markers and risk stratification:

In addition to basic cytogenetic analysis, molecular markers that can help refining prognostics groups, particularly in participants with a normal karyotype, include: NPM1, FLT3 (FLT3-ITD and FLT3-TKD), CEBPA, isocitrate dehydrogenase 1 and 2 (IDH1/2), DNA methyltransferase 3A (DNMT3A), c-KIT, MLL, TP53, RUNX1, and ASXL1 gene mutations (National Comprehensive Cancer Network (2021)).

16.6 Appendix 6: Statistical details on the Bayesian Logistic Regression Model (BLRM)

Details of the statistical model, the derivation of prior distributions from historical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios are included. A simulation study of the operating characteristics of the model is also presented.

16.6.1 Statistical model for single agent

The statistical model comprises a single-agent toxicity part for siremadlin, which allows the incorporation of single-agent toxicity information. The proposed statistical model uses a meta-analytic framework (Spiegelhalter et al 2004, Neuenschwander et al 2016) to combine all historical and concurrent data.

Let $\pi(d)$ be the risk of DLT for siremadlin given as a single agent dose at dose d. The single agent dose-DLT models are logistic:

$$\text{logit}(\pi(d))=\log(\alpha)+\beta \log(d/d^{*}) \quad (1)$$

where d^{*}, the reference dose, is used to scale the doses of siremadlin. The reference dose is defined in the appropriate model specifications sections.

Hence, α (>0) is the single-agent odds of a DLT at d^{*} and β (>0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

16.6.2 Prior specifications

The Bayesian approach requires the specification of prior distributions for the model parameters $\log(\alpha)$ and $\log(\beta)$. A meta-analytic framework approach was used to derive the prior distribution for these model parameters.

16.6.2.1 The meta-analytic framework approach

Assume we have data from historical or concurrent trials, which we want to use in combination with data in the new treatment arm.

Let $\pi_j(d_j)$ be the risk of single-agent DLT in group j (j = 1, ... , J) as defined in (1). A trial may consist of multiple groups, e.g, groups with different dose regimen.

The model assumes exchangeable parameters ("random effects"), and introduces a variance component accounting for between-group heterogeneity. Therefore, in order to borrow information across groups, an exchangeability structure is assumed across $\theta_j = (\log(\alpha_j),\log(\beta_j))$. $\theta_j \sim$ BVN (μ, Γ). $\mu = (\mu_\alpha, \mu_\beta)$ and Γ are the mean and between-group covariance matrix for the logistic parameters, the latter with standard deviations τ_α, τ_β and correlation ρ.

However, as historical studies may involve different regimens/patient population with concurrent studies, they can have different safety profile. Therefore, stratification between historical studies and concurrent studies is used to differentially discount data from each stratum through the covariance, with $s_j = 1, 2$ noting the stratum.

16.6.2.2 Prior specification

In Part 1, monotherapy of siremadlin is used. The Bayesian model consists of siremadlin single agent component.

Weakly informative priors are assumed for log(α) and log(β), with mean μ_α

equal to logit (0.15) corresponding to the anticipated DLT rate at the reference dose (d_1^*=siremadlin 150 mg corresponding to 30 mg QD Day 1-5 28-day cycle) and with mean μ_β

equal to 0 corresponding to a doubling in the dose of siremadlin leading to a doubling in the odds of the risk of a DLT. Priors for τ_1 and τ_2 are assigned such that (1) their medians correspond to large or moderate between trial heterogeneity for historical trials and concurrent trials respectively, and (2) their uncertainty (95% prior interval) cover plausible between trial standard deviations (Neuenschwander et al 2014). Full exchangeability is assumed.

The prior distributions for the model used for deriving the meta-analytic priors are specified in Table 16-8 below.

Table 16-8 Prior distributions for single-agent parameters

Parameter	Prior distribution
μ_α (Siremadlin)	N(mean = logit(0.15), sd = 2)
μ_β (Siremadlin)	N(mean = 0, sd=0.75)
$\tau_{\alpha 1}$ (Historical stratum)	log-normal(mean = 1, sd = log(4)/1.96)
$\tau_{\beta 1}$ (Historical stratum)	log-normal(mean = 0.5, sd = log(2)/1.96)
$\tau_{\alpha 2}$ (Concurrent stratum)	log-normal(mean = 0.25, sd = log(4)/1.96)
$\tau_{\beta 2}$ (Concurrent stratum)	log-normal(mean = 0.125, sd = log(2)/1.96)
ρ_1(Historical stratum)	uniform (-1,1)
ρ_2(Concurrent stratum)	uniform (-1,1)

16.6.2.3 Historical data

The prior described above was then updated by using the dose-DLT data from a Novartis study [CHDM201X2101] in post-SCT participants with AML treated with siremadlin single agent, and a Novartis study [CHDM201H12101C] in participants with AML or high-risk MDS treated with siremadlin in combination with sabatolimab. Historical data are presented in Table 16-9, andTable 16-10 . Data in the Novartis study [CHDM201H12101C] is assumed to be generated from siremadlin alone regardless of sabatolimab.

Table 16-9 Historical data from [CHDM201X2101] for siremadlin single agent

Siremadlin dose regimen	Number of participants for DDS	Number of participants with a DLT
250 mg Q3W*	3	1
350 mg Q3W*	1	0
400 mg Q3W*	2	2
120 mg QD on D1 and D8, 28-day cycle	2	0
150 mg QD on D1 and D8, 28-day cycle	1	0
20 mg QD 2 weeks on/ 2 weeks off	1	0
30 mg QD 2 weeks on/ 2 weeks off	1	0

*Doses are normalized to 28-day cycle

Table 16-10 Historical data from [CHDM201H12101C] for siremadlin and sabatolimab combination

Siremadlin dose regimen	Sabatolimab dose regimen	Number of participants for DDS	Number of participants with a DLT
20 mg QD Day 1 to 5, 28-day cycle	400 mg Q2W	4	0
40 mg QD Day 1 to 5, 28-day cycle	800 mg Q4W	4	0
40 mg QD Day 1 to 5, 28-day cycle	400 mg Q2W	3	0

16.6.2.4 Summary of prior distributions

The prior summaries for DLT rates are summarized in Table 16-11.

Table 16-11 Summary of prior distributions

Siremadlin QD dose	Prior probabilities that p(DLT) is in the interval:			Mean	SD	Quantiles		
	[0,0.16)	[0.,16,0.33)	[0.33,1]			2.5%	50%	97.5%
20 mg	0.971	0.025	0.004	0.037	0.050	0.001	0.020	0.172
30 mg	0.943	0.050	0.008	0.055	0.062	0.002	0.035	0.220
40 mg	0.894	0.093	0.013	0.074	0.075	0.004	0.051	0.275

16.6.2.5 Hypothetical dose scenarios for siremadlin single agent

To illustrate the performance of the model used to guide the dose escalation, hypothetical dose escalations scenarios are presented in Table 16-12. In each scenario, the recommended dose for the next cohort of participants is shown (dose escalation rules described in Section 6.6 of the study protocol).

Table 16-12 Probability of excessive toxicity estimated by the Bayesian model after each cohort

Scenario	Cohort	Siremadlin QD dose Day 1-5 (mg)	Number of		Siremadlin dose level for the next cohort	P(target toxicity) at highest siremadlin dose	P(excessive toxicity) at highest siremadlin dose
			Evaluable participants	DLTs*			
1	Cohort 1	30	3	1	40	0.244	0.047
2	Cohort 1	30	4	1	40	0.223	0.039
3	Cohort 1	30	5	1	40	0.204	0.023
4	Cohort 1	30	3	1	-	-	-
	Cohort 2	40	6	1	40	0.295	0.027
5	Cohort 1	30	3	1	-	-	-
	Cohort 2	40	6	2	40	0.484	0.098
6	Cohort 1	30	4	1	-	-	-
	Cohort 2	40	6	1	40	0.277	0.020
7	Cohort 1	30	4	1	-	-	-
	Cohort 2	40	6	2	40	0.466	0.084
8	Cohort 1	30	3	2	-	-	-
	Cohort 2	20	6	1	40	0.506	0.189
9	Cohort 1	30	3	2	-	-	-
	Cohort 2	20	6	1	-	-	-
	Cohort 3	40	6	2	40**	0.597	0.243

* Number of participants with at least one DLT.
** Probability of overdose at 20 mg is 0.042; probability of overdose at 30 mg is 0.121

16.6.3 Operating characteristics

16.6.3.1 Scenarios

In order to show how the design performs, four hypothetical scenarios are investigated:

- Scenario 1: True DLT rate is aligned to the mean of the prior distribution.
- Scenario 2: Higher toxicity profile for all the doses. True DLT rate of toxic doses is increased across the dose range.
- Scenario 3: Higher toxicity profile for all the doses and the last dose a much larger DLT rate than in scenario 1.
- Scenario 4: High toxicity profile for all the doses and all doses have excessive toxicity.

Hypothetical true DLT rate are shown in Table 16-13.

Table 16-13 Hypothetical true probabilities of DLT for different scenarios

Siremadlin QD dose Day 1-5 (mg)	Scenario			
	1. Prior means	2. Higher toxicity profile	3. Steep increase	4. High toxicity all
20	0.037	0.1	0.1	0.4
30	0.055	0.2	0.22	0.5
40	0.074	0.3	0.55	0.6

16.6.3.2 Simulation results

Operating characteristics are reviewed based on the simulation results under the four scenarios. The metrics reviewed are:

- Probability of participants receiving an overdose.
- Probability that identified RD at the end of the trial is in the target toxicity interval.
- Probability that identified RD is an overdose.
- Probability that identified RD is an underdose.
- Percentage of trials stopped without RD declaration.
- Average sample size.

Operating characteristics for the four scenarios are presented in Table 16-14.

Table 16-14 Operating characteristics for different true values of DLT rate *

Scenario	participants receiving an overdose	Probability to declare RD			Probability to stop for toxicity	Average sample size
		Over-dose	Target toxicity	Under-dose		
1. Prior means	0	0	0	1	0	10
2. Higher toxicity profile	0	0	0.956	0.022	0.022	15
3. Steep increase in toxicity for the last dose	0.450	0.288	0.449	0.115	0.148	20
4. High toxicity all doses	1	0.246	0	0	0.754	13

* Only evaluable participants. 1000 simulations were performed in R3.6.1 with option to de-escalate when >= 2 DLTs in a cohort are observed for the first time at that dose combination. In the simulated trials, first 3 participants were enrolled at the starting dose level of 30 mg. A second cohort of 3 participants was enrolled if 30 mg was maintained. If the decision was to escalate, a cohort of 6 participants was enrolled at 40 mg or another cohort of 6 participants at 20 mg if de-escalating. A dose level may be declared as RD after 6 participants were tested. The maximum number of participants was set at 100 for the simulation. Run time was 22:02 minutes.

16.7 Appendix 7: Statistical details on the Bayesian Time-to-DLT Model

Rationale of implementing the time-to-first-DLT approach is included as well as details of the statistical model, the derivation of prior distributions from historical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios. A simulation study of the operating characteristics of the model is also presented.

By the study design, if participants meet the eligibility criteria for DLI in Part 2, they will enter combination phase at the siremadlin dose tolerated in the last cycle of priming phase. The addition of DLI in the combination phase may increase the risk of GvHD. Participants may undergo different number of priming cycles and have acute or cumulative toxicities before entering the combination phase, which leads to changed population characteristics from the beginning of priming phase. Therefore, it is necessary to establish a safe maximum dose level for siremadlin in the combination phase which spans multiple cycles.

During combination phase, participants may receive up to 3 DLIs. The number of DLI cycles depends on various reasons besides DLTs. The DLIs will be administered in a ramp-up way starting with a relatively small dose. Thus, a conventional binomial model would be inadequate as it implies that the exposure time per participant is a single cycle only. Here we consider instead a multi-cycle model, which generalizes the binomial model. The multi-cycle model is realized as a simplified time-to-first-DLT model. Instead of a full time-to-event model, the time observation process is aligned with a respective binomial model in that time always lapses in at least full cycles. The model will be updated continuously with data when a cohort of 3 participants complete the first cycle of combination phase throughout the trial except the final assessment (for declaration of the maximum recommended dose for combination) will be conducted when the last participant in the final cohort completes the combination phase (below table). This approach allows participants to continue their treatment without operational interruptions and enables the close monitoring of all participants.

Table 16-15 Time point for the safety analysis in the combination Phase*

Safety assessment	Number evaluable participants	Timepoint	Decisions
1	3	The3rd participant has completed C1 or had a DLT	Maximum dose
2	(3 +) 3	The 6th participant has completed C1 or had a DLT	Maximum dose
3	(6 +) 3	The9th participant has completed C1 or had a DLT	Maximum dose
n	N	N participants have completed the combination phase	Declaration of maximum RD** (final assessment)

*There will be n safety assessments in total with N participants who enter combination phase.
** Declaration of maximum RD for combination requires at least 9 evaluable participants.

16.7.1 Statistical model

The statistical model is a piece-wise constant Poisson process, which is censored for each participant after the first event in case an event occurs. Each cycle defines a piece of the parametric hazard function. The model is specified via the instantaneous hazard h(t) which is transformed to the log scale to ensure positivity. As two independent factors contribute to the

overall DLT event rate in the combination phase, we use specifically a compound Poisson process. The siremadlin and DLI treatment contribute independently from each other to the overall event rate. For a compound Poisson process the total counting rate is the sum of the individual counting rates on the linear scale. Therefore we have

$Y_{m,n}$ = event counter for participant m in cycle n

$t_{m,n}$ = Time duration in days of cycle n of participant m

$Y_{m,n} \sim \text{Poisson}((\lambda_1 + \lambda_{2,n}) * t_{m,n})$

The linear predictor on the log-scale for the event counting rate for siremadlin is modelled with an intercept and positive slope as a function of the standardized dose of siremadlin

$\log(\lambda_1) = \alpha + \exp(\beta) * \log(d/d_{ref})$

, where d is siremadlin dose and d_{ref} is the siremadlin reference dose.

The DLI treatment is not modelled in dependence of a dose such that no slope is used. However, a cycle specific DLT event rate accounts for potential carry over effects of previous DLI treatments. The carry over effect reflects the ordering of the cycles through its structural form of

$\log(\lambda_{2,n}) = \gamma + I(n=2) * 2*\theta * x + I(n=3) *2* x,$

where γ is the overall intercept representing the DLI event rate in cycle 1, x being the average difference between cycles in the DLT event rate and θ being a percentage of the total Cycle 3 difference of 2 * x(modelled on the 0-1 scale).

The likelihood accounts for participants being in the risk set for each cycle as only terms are included in the likelihood for a given participant if still at risk of an event.

Importantly, time $t_{m,n}$ is being counted in at least full cycles for each participant. That is, the observation process is aligned with the commonly used binomial BLRM in that for each participant an exposure time of a full cycle is assumed. In consequence, $t_{m,n}$ is always at least 42 days (6 weeks) for any participant and cycle. The exact value of $t_{m,n}$ depends on the start of the follow-up cycle n+1, which is determined by constraints of the clinical context of the participant.

16.7.2 Prior specifications

The Bayesian approach requires the specification of prior distributions for the model parameters. A meta-analytic framework approach was used to derive the prior distribution for these model parameters.

Table 16-16 Prior distributions for single-agent and interaction parameters

Parameter	Prior distribution
$\mu_{1\alpha}$ (siremadlin)	N(mean = -6.7, sd = 2.5)
$\mu_{1\beta}$ (siremadlin)	N(mean = 0, sd = 1)
$\mu_{2\alpha}$ (DLI)	N(mean = -6.1, sd = 2.5)
$t_{1\alpha1}$, $t_{2\alpha1}$	log-normal(mean = log(2.5/4.0), sd = log(2)/1.96)
$t_{1\beta1}$	log-normal(mean = log(2.5/8.0), sd = log(2)/1.96)
x	N(mean = 0, sd = 1)
θ	Beta(alpha = 1, beta = 1)

16.7.2.1 Historical data

The prior described above was then updated by using the dose-DLT data in Section 16.6.2.3 as well an external study (Guillaume et al 2019) where post-allo-SCT HR AML and HR MDS participants treated with azacitidine and DLI. Historical data are presented in Table 16-9, Table 16-10 and Table 16-17. Data in the Guillaume study is assumed to be generated from DLI alone regardless of azacitidine.

Table 16-17 Historical data from [Guillaume et al (2019)] for DLI

DLI*	DLI received	Number participants	Number participants with DLT
Cycle 1	1	17	2
Cycle 2	1	12	0
Cycle 3	1	10	0

*DLI is given1 per cycle of 8 weeks with 3 DLIs of 5e6 CD3+/kg, 1e7 CD3+/kg and 5e7 CD3+/kg for matched related donors and 1e6 CD3+/kg, 5e6 CD3+/kg and 1e7 CD3+/kg for matched unrelated donors.

16.7.2.2 Summary of prior distributions

The prior summaries for DLT rates are summarized in Table 16-18.

Table 16-18 Summary of prior distributions

Siremadlin QD dose	Cycle number	DLT rate		Quantiles / (%)		
		Mean/(%)	SD/(%)	25%	50%	75%
20 mg	1	13.1	13.5	4.5	8.8	16.7
20 mg	2	8.4	10.2	2.3	5.0	10.6
20 mg	3	7.1	9.8	1.4	3.7	8.7
30 mg	1	15.4	14.3	6.0	11.0	19.9
30 mg	2	10.9	11.7	3.4	7.2	14.0
30 mg	3	9.6	11.4	2.6	5.8	12.5
40 mg	1	19.1	16.0	8.0	14.5	24.5
40 mg	2	14.7	14.2	5.3	10.1	19.2
40 mg	3	13.5	14.0	4.2	8.8	17.8

16.7.2.3 Hypothetical dose scenarios for siremadlin/DLI combination

To illustrate the performance of the model used to guide the dose escalation, hypothetical dose escalations scenarios are presented in Table 16-19. In each scenario, the maximum dose for the next cohort of participants is shown (dose escalation rules described in Section 6.6 of the study protocol).

Table 16-19 Predicted DLT rate estimated by the Bayesian model after each cohort

Scenario	Cohort	Siremadlin QD dose Day 1-5 (mg)	#evaluable participants	#DLTs	Siremadlin dose level for next cohort	Cycle number	Mean DLT rate at highest siremadlin dose	75th percentile
1	Cohort 1	30	3	1	40	1	0.220	0.288
						2	0.170	0.225

Scenario	Cohort	Siremadlin QD dose Day 1-5 (mg)	#evaluable participants	#DLTs	Siremadlin dose level for next cohort	Cycle number	Mean DLT rate at highest siremadlin dose	75th percentile
						3	0.155	0.207
2	Cohort 1	30	3	2	20	1	0.237	0.317
						2	0.154	0.213
						3	0.128	0.181
3	Cohort 1	30	2	1	40	1	0.212	0.276
		40	1	0		2	0.161	0.214
						3	0.145	0.193

16.7.3 Operating characteristics

16.7.3.1 Scenarios

In order to show how the design performs, four hypothetical scenarios are investigated:

- Scenario 1: True DLT rate is aligned to the mean of the prior distribution.
- Scenario 2: Higher toxicity profile for all the doses. True DLT rate of toxic doses is increased across the dose range.
- Scenario 3: Higher toxicity profile for all the doses and the last dose a much larger DLT rate than in scenario 1.
- Scenario 4: High toxicity profile for all the doses and all doses have excessive toxicity.

Constant DLT rates were assumed over the 3 cycles. Hypothetical true DLT rate are shown in Table 16-20.

Table 16-20 Hypothetical true probabilities of DLT for different scenarios

Siremadlin QD dose Day 1-5 (mg)	Scenario			
	1. Prior means	2. Higher toxicity profile	3. Steep increase	4. High toxicity all
20	0.13	0.21	0.15	0.4
30	0.152	0.28	0.23	0.5
40	0.183	0.38	0.5	0.6

16.7.3.2 Simulation results

Operating characteristics are reviewed based on the simulation results under the four scenarios. The metrics reviewed are:

- Probability of participants receiving an overdose.
- Probability that identified maximum RD at the end of the trial is an overdose.
- Probability that the trial is stopped early due to toxicity.
- Probability that the trial reaches maximum number of participants without declaring a maximum RD.

- Average sample size.

At least 9 evaluable participants are required to determine the maximum recommended dose of siremadlin in combination with DLI. A dose level to be declared as maximum RD for combination must be tested with at least 3 evaluable participants treated at or above that dose level. However, the actual number of evaluable participants is not known. Thus, operating characteristics for the four scenarios are presented for 9 and 18 evaluable participants in Table 16-21 and Table 16-22 respectively.

Table 16-21 Operating characteristics for different true values of DLT rate for n=9 patients *

Scenario	Participants receiving an overdose	Probability of the declared maximum RD being an OD	Probability to stop for toxicity	Probability of inconclusive results	Average sample size
1. Prior means	0.0	0.0	0.035	0	8.826
2. Higher toxicity profile	2.195	0.244	0.15	0.019	8.43
3. Steep increase	2.23	0.214	0.117	0.016	8.538
4. High toxicity all	6.735	0.289	0.687	0.024	6.735

* Only evaluable participants. 1000 simulations were performed in R3.6.1

Table 16-22 Operating characteristics for different true values of DLT rate based on n=18 patients*

Scenario	Participants receiving an overdose	Probability of the declared maximum RD being an OD	Probability to stop for toxicity	Probability of inconclusive results	Average sample size
1. Prior means	0.0	0.0	0.036	0	17.505
2. Higher toxicity profile	3.503	0.306	0.187	0.002	15.933
3. Steep increase	3.597	0.325	0.127	0	16.443
4. High toxicity all	8.943	0.15	0.850	0	8.943

* Only evaluable participants. 1000 simulations were performed in R3.6.1