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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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
aGvHD	Acute Graft versus Host Disease
Allo-SCT	Allogeneic Stem Cell Transplantation
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic classification
AUC	Area under the curve
BLRM	Bayesian Logistic Regression Model
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CI	Confidence interval
cGvHD	Chronic Graft versus Host Disease
CR	Complete remission
CRi	Complete remission with incomplete hematologic recovery
CRF	Case report form
CSR	Clinical study report
CTC	Common toxicity criteria
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
CV	Coefficient of variation
DDS	Dose-determining set
DLI	Donor lymphocyte infusion
DLT	Dose limiting toxicity
DMS	Document management system
eCRF	Electronic case report form
eCRS	Electronic case retrieval strategy
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
ELN	European Leukemia Net
EOT	End of treatment
EWOC	Escalation with overdose control
FAS	Full analysis set
G-CSF	Granulocyte colony stimulating factor
[redacted]	[redacted]
HR	High risk
IA	Interim analyses
IRT	Interactive response technology
MedDRA	Medical Dictionary for Drug Regulatory Affairs
[redacted]	[redacted]
OS	Overall survival
PAS	Pharmacokinetic analysis set

PD	Progressive disease
PK	Pharmacokinetic(s)
PR	Partial response/remission
PT	Preferred term
QD	Latin abbreviation for every day
RAP	Report and analysis process
RBC	Red blood cells
RD	Recommended dose
RFS	Relapse free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SMQ	Standardized MedDRA queries
SOC	System organ class
SoC	Standard of Care
TP53	Tumor protein P53
TFLs	Tables, figures, listings
TLS	Tumor lysis syndrome
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes the planned analyses for the Clinical Study Report (CSR) of the study CHDM201K12201, a phase Ib/II, open label, proof of concept study of siremadlin in combination with donor lymphocyte infusion (DLI) as a treatment for patients with acute myeloid leukemia (AML) post-allogeneic stem cell transplantation (allo-SCT) who are in complete remission but at high risk for relapse.

The content of this SAP is based on the CHDM201K12201 Protocol Amendment 2 (release date: 18-Nov-2022). All decisions regarding the analysis, as defined in the SAP document, were made prior to database lock.

As specified in Section 12.7 of the study protocol, no formal interim analyses are planned. The monitoring of safety data was planned to be conducted after each dose level cohort of the siremadlin monotherapy in Part 1 as well as after each cohort of 3 participants who completed at least one siremadlin/DLI treatment cycle in combination phase in Part 2. This SAP served as the basis for those analyses as well. A separate selection of tables, figures, and listings (TFLs) will be provided. The first safety review meeting was held on 18-Sep-2023 for Cohort 1 at siremadlin monotherapy 30 mg QD Days 1-5 of a 28-day cycle, where no new safety concern was identified.

However, Novartis decided to permanently halt the recruitment of new participants into study CHDM201K12201 in September 2023 (recruitment halt letter dated 21-Sep-2023 was sent to investigators on 25-Sep-2023). As a result, Part 1 was discontinued after the Cohort 1 safety review meeting, and Part 2 of the study will not be opened. This decision was not based on any safety findings or safety concerns with siremadlin but rather on a Novartis strategic consideration. The decision about the permanent recruitment halt was documented in the Early Termination Plan for the study. The study data will be analyzed and reported based on all available data up to the data cut-off date of the final DBL in a synoptic final CSR.

1.1 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 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 Protocol 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) :

- **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 dose limiting toxicity (DLT) rate, overall safety, tolerability, available pharmacokinetic (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 in Part 1, 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).

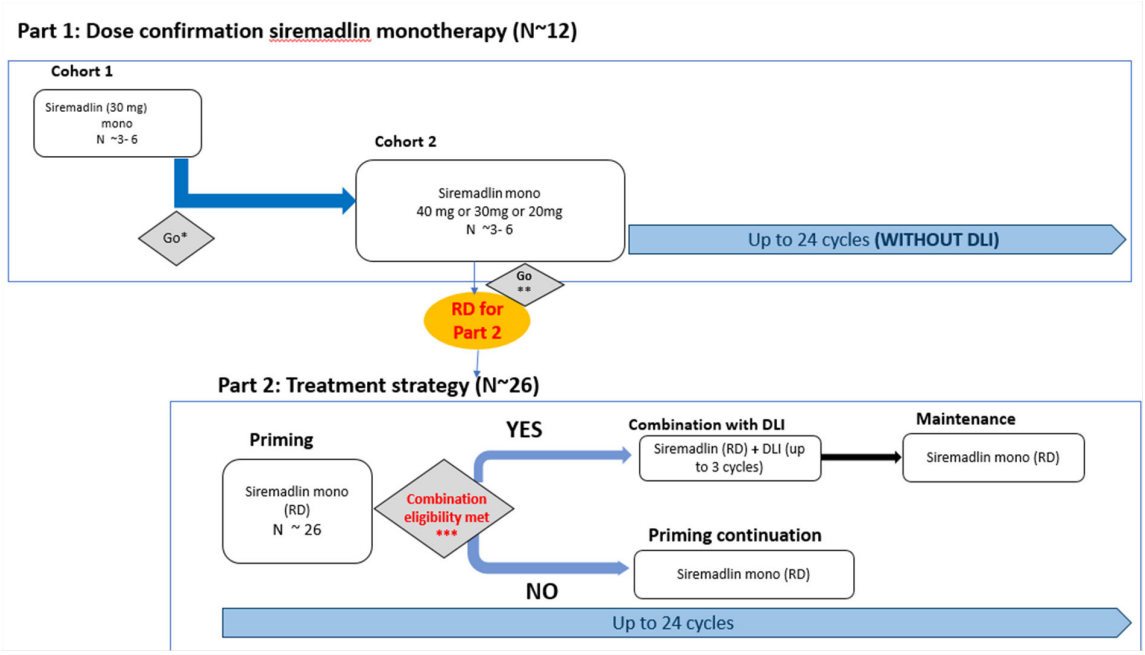
Once the recommended siremadlin dose is determined in Part 1, enrollment in Part 2 will start after obtaining Health Authority's approval as applicable. Enrollment in Part 2 will not be applicable to the participating sites in the United States and Germany.

- **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 1.1):
  - 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 Protocol 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 Protocol 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 Protocol 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 Protocol 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 1-1 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 Protocol 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, participants 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 Protocol Section 6.6.2 for details)

1.2 Study objectives, endpoints and estimands

Table 1-1 (which is a copy of the Table 2-1 from the study protocol) outlines the primary, secondary [redacted] objectives and belonging endpoints. Due to the permanent recruitment halt for Part 1 and Part 2, only the first cohort of participants treated at siremadlin 30 mg monotherapy in Part 1 was completed, and the recommended siremadlin dose was not determined in Part 1. Consequently, only primary and secondary objectives for Part 1 will be analyzed for the synoptic CSR, excluding time to event endpoints which require the recommended siremadlin dose (as further detailed in Section 2). All primary and secondary objectives for Part 2 will not be analyzed [redacted]

Table 1-1 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].	● Incidence of DLTs with siremadlin monotherapy in dose confirmation [Part 1]
● 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].	● 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.

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Objective(s)	Endpoint(s)
● 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.
● 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]

1.2.1 Primary estimand(s)

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 (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 (Part 1) 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 the 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. (Refer to Protocol 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 (in Part 2):

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 siremadlin priming phase and meet combination phase eligibility to receive DLI as defined in Protocol 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, when administered in combination with DLI.
4. Handling of remaining intercurrent events:
    - Dose modifications, dose interruptions or discontinuations due to reasons other than DLT leading to less than minimum exposure:
        - 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).
    - End of combination phase without experiencing DLT: participants will be censored at the last safety assessment in the combination phase.
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 Protocol 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 participating in Part 2 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 Protocol 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.

1.2.2 Secondary estimand

Not applicable

2 Statistical methods

2.1 Data analysis general information

The primary analysis, as well as the analyses that will be used for the safety review meetings of the Part 1 and combination phase of the Part 2 of the study will be performed by Novartis.

SAS 9.4 (or higher version) or R 3.6.1 (or higher version) will be used to perform all data analyses and to generate tables, figures, and listings.

The study data will be analyzed and reported based on all available data up to the cut-off date of the final DBL in a synoptic final CSR.

General analysis conventions

Qualitative data (e.g., gender, race) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of participants in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight) will be summarized by appropriate descriptive statistics (e.g., mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum).

Data included in the analysis / data cut-off handling

For each of the safety review meetings in Part 1, a data cut-off date will be determined after the targeted number of participants has completed 1 cycle of treatment. All safety data (including duration of exposure to study treatment, dose modifications, study treatment discontinuation, etc.), demographics, disease history (including cytogenetics, risk category, acute/chronic GvHD, etc.), concomitant medications, hematology data, extramedullary disease assessment, blast counts from bone marrow and PK data (if available) with an assessment date or event start date (e.g., laboratory assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. The list of analyses to be presented at the time of the safety review meetings is provided in Section 2.13.

For the synoptic CSR, all data collected up to the cut-off date of the final DBL will be included in the analysis.

2.1.1 General definitions

Both "*Investigational drug*" and *"Study treatment"* refer to siremadlin.

Donor Lymphocyte Infusion (DLI)

DLI given in combination phase of Part 2 is not a part of the study treatment and should be administered according to standard local clinical practice or institutional guidelines. However, 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.

Date of first administration of study treatment

The date of the first administration of study treatment is defined as the first date when a non-zero dose of the respective study treatment is administered and recorded on the study treatment eCRF page.

Date of last administration of study treatment

The date of the last administration of the study treatment is defined as the last date when a non-zero dose of the respective study treatment is administered and recorded on the study treatment eCRF page.

Study day

The study day describes the day of the event or assessment date, relative to the reference start date (start date of study treatment).

The study day is calculated as follows:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g., adverse event onset, laboratory or ECG assessment, vital sign measurement) is the start of study treatment. The same reference start date will be used for efficacy (e.g., response assessment, time-to-event endpoints).

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Baseline

For efficacy evaluations, the last non-missing assessment post-allo-SCT, including unscheduled assessments on or within 28 days before the date of start of study treatment is taken as “baseline” value or “baseline” assessment.

For safety evaluations, the last available assessment including unscheduled assessments on or before the date of start of study treatment is taken as “baseline” assessment.

If participants have no value as defined above, the baseline result will be missing.

Last contact date

The last contact date will be used for censoring of participants in the analysis of relapse free survival and overall survival.

The last contact date is defined as the latest complete date from the below list on or before the data cut-off date (Table 2-1). The cut-off date will not be used for last contact date unless the participant was seen or contacted on that date. No date post cut-off date will be used.

Completely imputed dates (e.g., the analysis cut-off date programmatically imputed to replace the missing end date of a dose record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring only if coming from the 'Survival' eCRF.

The last contact date will be derived for participants not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-1 Last contact date data sources

Source data	Conditions
Last date participant was known to be alive from Survival Follow-up page	Participant status is reported to be alive or unknown
Start/End dates from antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from drug administration record	Non-missing dose
Response assessment date	Response marked as 'done'
Laboratory/PK collection dates	Sample collection marked as 'done'
Vital signs date	At least one non-missing parameter value
ECOG performance status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

Other general definitions are detailed in Appendix Section 5.1.

2.2 Analysis sets

The Full Analysis Set (FAS) comprises all participants who 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, met the minimum exposure criteria (MEC), met the minimum follow up/ DLT observation after treatment and have sufficient safety evaluations, or have experienced a DLT during the observation period.

MEC for Part 1 (MEC1) is defined as a participant who has received, during the first cycle, at least 75% of the total planned doses of siremadlin (e.g., ≥ 4 out of 5 daily doses of siremadlin).

MEC for Part 2 (MEC2) is defined as a participant who has received at least one dose of DLI and at least 75% of the total planned doses of siremadlin for a given combination cycle.

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

- DDS1 (siremadlin monotherapy in Part 1): consists of participants from each siremadlin dose level cohort who met the MEC1, met the minimum DLT observation period and had sufficient safety evaluations, or had a DLT during Cycle 1. Participants receiving a reduced dose of siremadlin due to co-administration of strong or moderate CYP3A4 inhibitors as

described in Protocol Section 6.2.1.1, will be considered to have received the full planned dose.

DLT observation period for DDS1 starts from the first dose administration of siremadlin (Cycle 1 Day 1) until the end of Cycle 1 (planned on Cycle 1 Day 28):

- For participants who started Cycle 2, the end of the DLT observation period will be the day before the initiation of Cycle 2 Day 1 (whatever the status of the patient: on-treatment or on drug interruption period).
- For participants who did not start Cycle 2, the end of the DLT observation period will be Cycle 1 Day 28 or the last on-treatment day within Cycle 1 (up to 42 days after Cycle 1 Day 1), whichever comes later.

Participants who do not experience a DLT during Cycle 1 are considered to have sufficient safety evaluations if they have met the DLT observation period in Cycle 1 (as defined above), 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, met the minimum DLT observation period after treatment and had sufficient safety evaluations, or had a DLT during combination phase. Participants receiving a reduced dose of siremadlin due to co-administration of strong or moderate CYP3A4 inhibitors as described in Protocol Section 6.2.1.1, will be considered to have received the full planned dose.

  DLT observation period for DDS2 starts from the first study treatment or first DLI administration during the first combination cycle until the end of combination Phase (Day 42 of the last combination cycle) [i.e., over the entire siremadlin/DLI combination phase].

  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 met the DLT observation period (as defined above), and are considered by both the sponsor and investigators to have enough safety data to conclude that a DLT did not occur. For a participant who experiences a DLT prior to the first DLI in the first cycle of their combination phase, this DLT will be assigned to siremadlin monotherapy. However, for subsequent combination cycles, if a DLT occurs before the DLI has been received, the DLT attribution to the earlier combination cycle will be evaluated. 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.

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 Protocol 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.

2.2.1 Subgroup of interest

No specific subgroups of interest will be considered for the synoptic CSR.

2.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for the analyses below. Participant disposition, demographics and other baseline characteristics will be summarized by dose level of siremadlin for participants in Part 1.

2.3.1 Patient disposition

Number (%) of participants screened and enrolled will be summarized by country and center. For participants who did not complete screening, the reasons for not completing screening will be summarized based on "Screening Phase" page in "Disposition" eCRF.

The number (%) of participants in the FAS who started treatment, are still on treatment, who entered and discontinued post-treatment follow-up and the study after survival follow-up will be summarized together with the respective reasons for discontinuation from treatment/post-treatment follow-up/end of study (which corresponds to end of survival follow-up). The number (%) of participants by dose level of siremadlin in Part 1will be also summarized.

The number (%) of participants in the FAS with any protocol deviation will be tabulated by deviation category. All protocol deviations will be listed.

2.3.2 Demographics and other baseline characteristics

Demographic (age, sex, country, ethnicity, race and Eastern Cooperative Oncology Group (ECOG)) performance status and other baseline data including disease characteristics will be listed and summarized descriptively for all participants from the FAS. The summary by dose level of siremadlin in Part 1will be provided.

BMI (kg/m^2) at baseline will be calculated as weight[kg] / (height[m]²) using weight at baseline and height at screening. Body Surface Area (BSA) is based on the Mosteller formula described below:

$$\text{BSA } (m^2) = \sqrt{\text{Weight (kg)} * \text{Height at screening (cm)}/3600}$$

Details on AML diagnosis / disease history [date of initial diagnosis, WHO classification, ELN classification (Döhner et al 2017), cytogenetic abnormalities, and molecular genetic abnormalities] will be listed and summarized.

Allogeneic transplant characteristics (disease remission status at time of transplant, transplantation timing, donor type, donor-host HLA match) will be tabulated and time since transplant will be listed.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The

MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable outputs.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment and DLI / compliance

The Safety set will be used for the analyses below and summary tables will be presented by dose level of siremadlin in part 1. "Cycle(s)" in this document refers to the cycle(s) with at least one non-zero dose of any study treatment. 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

Duration of exposure

The duration of exposure (in months) will be summarized for study treatment based on summary statistics and categorical analyses. Details on start and end dates used for derivations are outlined in Section 5.1.

Cumulative dose

For siremadlin, the actual cumulative dose in mg is the sum of "dose administered -Siremadlin" from the eCRF of all cycles during the exposure to siremadlin.

Dose intensity and relative dose intensity

Dose intensity is defined for participants with non-zero duration of exposure. For participants who did not take the drug, the dose intensity is by definition equal to zero. The actual dose intensity is computed as the ratio of actual cumulative dose received and duration in days from first to last cycle.

The planned dose intensity for siremadlin is computed as the ratio of planned cumulative dose in a cycle over the duration in days from first to last cycle [42 days for each combination cycle in Part 2, and 28 days for each siremadlin monotherapy cycle in Part 1 or Part 2].

The relative dose intensity is then computed as the ratio of actual dose intensity and planned dose intensity.

As an example, if a participant received siremadlin at 25 mg QD D1-D5 on average throughout the study (instead of the 30 mg QD D1-D5 as planned per protocol, which corresponds to a planned dose intensity of 150 mg/28 days), the relative dose intensity for this participant is 0.83.

Participants receiving a reduced dose of siremadlin due to co-administration of strong or moderate CYP3A inhibitors as described in Protocol Section 6.2.1.1, will be considered to have received the full planned siremadlin dose.

Details on the duration in days from the first to last cycle for the derivation of the dose intensity and the relative dose intensity are provided in Appendix Section 5.1.

Dose reduction, dose interruption and permanent discontinuations

The number (%) of participants with any dose changes (incl. reductions, interruptions, or permanent discontinuations) and the reasons (e.g., AE, dosing error, dispensing error) will be taken from the eCRF "Study Treatment Siremadlin" and summarized. The total duration of interruptions by participant will be summarized for the study population by time intervals, e.g., <1week, ≥1-<2 weeks, ≥2-<3 week, etc. (these time intervals may be adjusted depending on the observed data).

Cycle initiated

The number of cycles initiated by a participant will be summarized. A cycle is delayed if the first dose of study treatment within a cycle is administered > 3 days after the scheduled date. For the eCRF, a cycle delay will be recorded as a dose interruption between the planned start date of the cycle and the day before the actual date of the first dose of any study treatment within the cycle.

2.4.2 Prior, concomitant and post therapies

Prior or concomitant medications and significant non-drug therapies within 28 of starting study treatment until 30 days after the last dose of siremadlin will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

Prior anti-neoplastic medications/radiotherapy will be summarized using the FAS. Medications will be summarized by ATC class and preferred term.

Anti-neoplastic therapies after discontinuation of study treatment during follow-up within the study will be listed using the FAS by ATC class and preferred term.

All transfusions of blood products (incl. those not related to AML) prior (during screening) and after start of study treatment will be listed using the FAS.

2.5 Analysis supporting primary objective(s)

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.

2.5.1 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 DDS1 or DDS2. The definition of DLT evaluation period is defined in Section 5.1 and the details of DLT are defined in Protocol Section 6.6.3 which are captured in eCRF.

The primary efficacy endpoint of the study is the proportion of participants who are alive and remain in CR/CRi at least 6 months after the of start study treatment among participants who

initiated priming phase at the siremadlin RD for priming in Part 2 (Cheson et al 2003, Döhner et al 2017). Details on the definition of response categories which are to be captured in the eCRF by the investigator were defined in the Study Protocol Table 8-4 that was copied into Table 2-2.

Table 2-2 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	Bone marrow: • < 5% blasts • no blasts with Auer rods Peripheral blood: • neutrophils ≥ $1.0x10^9$/L • platelets ≥ $100x10^9$/L • no circulating blasts No evidence of extramedullary disease (such as CNS or soft tissue involvement).
Complete remission with incomplete hematologic recovery (CRi)	Bone marrow: • < 5% blasts • no blasts with Auer rods Peripheral blood: • neutrophils < $1.0x10^9$/L or platelets < $100x10^9$/L • no circulating blasts No evidence of extramedullary disease (such as CNS or soft tissue involvement).
Relapse from CR or CRi	Only in participants with a CR or CRi. Any of the following: • Reappearance of blasts in peripheral blood **OR** • ≥ 5% blasts in bone marrow **OR** • (Re-)appearance 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	

2.5.2 Statistical hypothesis, model, and method of analysis

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

As Novartis decided to permanently halt the enrollment and consequently, Part 2 was not opened, time-to-DLT analysis will not be performed for the synoptic CSR.

For participants in the Cycle 1 of Part 1, assessing whether siremadlin at the tested dose levels does not lead to an unacceptable level of toxicity (DLTs) when administered as monotherapy will be based on the estimation of the probability of DLT within the DLT evaluation period for participants in the DDS1. The assessment will be guided by a Bayesian analysis of DLT data for siremadlin monotherapy within the DLT evaluation period of treatment. The probability of

DLT is modeled using a Bayesian approach detailed in the Study Protocol Appendix Section 16.1.

After each cohort in Part 1 is completed, posterior distributions for the risk of DLT will be summarized to provide the posterior probability that the risk of excessive toxicity (DLT rate ≥ 33%) is less than 25% (Escalation with Overdose Control (EWOC) principle, Babb et al 1998).

The standard EWOC defines overdosing as the probability of having a DLT >33% and limits the probability of overdosing under 25% (i.e., probability to observe a DLT rate exceeding 33% is below 25%).

A full assessment of the prior risk to participants and a summary of the operating characteristics of the models is given in Protocol Section 16.6

For participants who complete the 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 in combination with DLI will be based on the estimation of the probability of DLT for participants in the DDS2 for combination phase in Part 2. 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.

The standard EWOC defines overdosing as the probability of having a DLT >33% and limits the probability of overdosing under 25% (i.e., probability to observe a DLT rate exceeding 33% is below 25%). The conditional probabilities (given that the patient made it to the start of that cycle without a DLT) of overdosing/target/underdosing probabilities per-cycle will be summarized.

A full assessment of the prior risk to participants and a summary of the operating characteristics of the models is given in Protocol Section 16.7.

Primary efficacy analysis (proportion of participants who remain in CR/CRi 6 months after the start of study treatment) (in Part 2)

As Novartis decided to permanently halt the enrollment and consequently, Part 2 was not opened, this primary efficacy analysis will not be performed for the synoptic CSR.

The efficacy of study treatment will be based on the proportion of participants in Part 2 remaining in CR/CRi as per investigator assessment for at least 6 months after the start study treatment among participants who initiated priming phase at the siremadlin RD for priming with/without DLI. Assuming a minimally informative prior distribution (Beta(0.67,1)) with mean 40% based on the null value 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)

2.5.3 Handling of intercurrent events

Handling of intercurrent events of the primary efficacy and safety estimands is described in Section 1.2.1

2.5.4 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.

2.5.5 Sensitivity analyses

Not applicable

2.5.6 Supplementary analyses

Not applicable

2.6 Analysis supporting secondary objectives

The secondary objectives for Part 1 and Part 2 are to assess the effect of siremadlin with/without DLI on safety and tolerability, cumulative incidence of relapse, proportion of participants stopping study treatment due to GvHD/AE, incidence of treatment-emergent grade III/IV aGvHD and moderate/severe cGvHD, 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 (in participants treated at the RD for Part 2) on prevention of hematologic relapse. Secondary objectives for Part 2 only are relapse free survival (RFS) and overall survival (OS).

2.6.1 Secondary endpoint(s)

Efficacy endpoints will be analyzed and summarized in FAS and by dose level of siremadlin in Part 1 unless otherwise specified. Responses per investigator assessment (Table 2-2) will be used unless specified otherwise.

Time-to-event endpoints will not be analyzed given siremadlin RD for priming was not determined and Part 2 was not opened.

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) [Part 2 only]

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:

1. the analysis cut-off date, and
2. 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 1.2.1).

Cumulative incidence of relapse [Part 1 and 2]

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 occur between:

1. the analysis cut-off date, and
2. the date when a new anti-neoplastic therapy is started. The censoring date will be the date of the last adequate response assessment.

Overall Survival (OS) [Part 2 only]

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.

GvHD-free/relapse-free survival (GRFS) [Parts 1 and 2]

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:

1. the analysis cut-off date, and
2. the date when a new anti-neoplastic therapy is started. The censoring date will be the date of the last GvHD assessment given confirmed remission in a subsequent efficacy assessment. The details of aGvHD and cGvHD are defined in Study Protocol Section 16.1 and Section 16.2 which are captured in eCRF page.

Participants remaining in CR/CRi (in Part 1)

The participants who remain in CR/CRi at least 6 months after the start of study treatment among participants in Part 1 treated with siremadlin monotherapy at the recommended dose for Part 2 will be listed.

Handling of intercurrent events will follow the same rule in the primary efficacy estimand.

2.6.2 Sensitivity analyses

Not applicable

2.6.3 Supplementary analyses

Not applicable

2.7 Safety analyses [Part 1]

Safety analyses will be summarized for the Safety Set by dose level of siremadlin in Part 1.

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:

1. Pre-treatment period: from day of participant's informed consent to the day before first administration of study treatment
2. On-treatment period: from date of first administration of study treatment to 30 days after date of last administration of study treatment
3. Post-treatment period: any observation starting at day 31 after last administration of study treatment

2.7.1 Adverse events (AEs)

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 (SOC), preferred term (PT) and maximum severity. A participant with multiple occurrences of an AE will be counted only once in the respective AE category. A participant with multiple CTCAE grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event. AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

In the AE summaries, the primary SOC will be presented alphabetically, and the PT will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency in the “overall” column (combining all dose levels of siremadlin). The summaries will show ‘All grades’ (including AEs with missing grade) and ‘Grades ≥ 3’.

The following adverse event summaries will be produced selecting all or a subset of AEs depending on seriousness, relationship to study treatment, outcome or action taken:

- AEs (by SOC and by PT) and separately those considered related to study treatment
- SAEs and separately those considered related to study treatment

- SAEs with number of occurrences (an occurrence is defined as >1 day between start and prior end date of record of same PT)
- Non-SAEs
- SAEs with fatal outcome and separately those considered related to study treatment
- AEs leading to permanent study treatment discontinuation by study treatment
- AEs leading to dose adjustment/interruption
- AEs requiring additional therapy

All reported AEs will be listed and those that started during the pre-treatment, and post-treatment period will be flagged.

Acute GvHD and chronic GvHD will be listed separately. Post-treatment period will be flagged.

For the legal requirements of ClinicalTrials.gov and EudraCT, two tables on on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and on on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a patient several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of th consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of on-treatment deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to siremadlin. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized MedDRA queries (CMQs) and/or Novartis MedDRA queries (NMQs) may also be used. These are customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. These searches will be defined in the eCRS (electronic Case Retrieval Sheet) and a listing of search terms will be provided in the DMS (Document Management System). The eCRS version used events retrieval will be specified as a footnote in the applicable outputs.

For each specified AESI, the number (%) of participants with at least one event of the AESI occurring during the on treatment period will be summarized together with the individual preferred terms in that grouping. In addition, number (%) of participants with at least one AESIs by maximum CTCAE grade, related AESIs, serious AESIs as well as action taken and outcome of the respective AESI will be summarized.

2.7.2 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment deaths not in the AE CRF but in the survival CRF) will be produced showing deaths reasons by primary reason and PT. All deaths will be listed for all screened participants. Post treatment deaths and prior to starting treatment death will be flagged.

2.7.3 Laboratory data

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 classification to compare baseline to the worst on-treatment value

Liver function parameters of interest are total bilirubin, Direct Bilirubin, ALT, AST, gamma-glutamyl transferase (GGT) and alkaline phosphatase. The number (%) of participants with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

All CTCAE grade ≥ 3 laboratory toxicities will be flagged.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

ECGs are collected as 12-lead triplicate using the ECG machines supplied by the central laboratory and then transmitted electronically to the central laboratory for central review by an independent reviewer.

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. If a participant has more than one measurement at a specific time point, the average of all available measurements associated with the nominal time point will be used for the analyses.

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

Notable ECG values during on-treatment period in participants with normal values at baseline (for the respective QTc value) will be summarized using the following criteria:

Table 2-3 Notable ECG values

ECG parameter (unit)	Clinically notable criteria
QTcF (ms)	Increase >30 and ≤ 60 ms
	Increase >60 ms
	New >450 to ≤ 480 ms
	New >480 to ≤ 500 ms
	New >500 ms
HR (bpm)	Increase >25% and HR >100 bpm
	Decrease >25% and HR<50 bpm

2.7.4.2 Vital signs

Notable vital sign values during on-treatment period will be summarized using the following criteria:

Table 2-4 Notable vital sign values

Vital sign (unit)	Clinically notable criteria	
	above normal value	below normal value
Systolic blood pressure (mmHg)	≥ 180 with increase from baseline of ≥20	≤ 90 with decrease from baseline of ≥20
Diastolic blood pressure (mmHg)	≥105 with increase from baseline of ≥15	≤ 50 with decrease from baseline of ≥15
Pulse rate (bpm)	≥100 with increase from baseline of >25%	≤ 50 with decrease from baseline of > 25%
Weight (kg)	Increase ≥10% from baseline	Decrease ≥ 10% from baseline
Body Temperature	>=39.1 °C	

2.7.4.3 ECOG PS

ECOG PS categorical data will be displayed by timepoint in listing.

2.8 Pharmacokinetic endpoints

The PAS-all will be used in all pharmacokinetic data analysis.

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 2-5 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 2-5 Non-compartmental pharmacokinetic parameters*

AUC0-t	The area under the concentration vs. time Curve (AUC) from time zero to specified time point. Note: when the last sampling time of the PK profiles at Cycle 1 Day 1 is 24h post-dose (in CONF or PRIM), 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 8-10a and Table 8-10b.

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

Siremadlin concentration data will be listed by participant, by dose level of siremadlin, and by Cycle/Day, sampling time point (See Protocol Section 8.5.1 for details). Descriptive summary statistics for siremadlin concentrations will be provided by dose level of siremadlin, by Cycle/Day, /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.

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

Not applicable

2.11 Biomarkers

Not applicable.

2.12 Other Exploratory analyses

Not applicable.

2.13 Interim analysis

No formal interim analysis is planned for this trial.

However, safety review meetings will be conducted after each dose level cohort of the siremadlin monotherapy in Part 1 as well as after each cohort of 3 participants who completed at least one siremadlin/DLI treatment cycle in combination phase in Part 2.

The decision to start enrollment in the subsequent cohort and to continue with the siremadlin RDE in the expansion phase will be guided by a Bayesian analysis based on the incidence of DLT data.

For each cohort of the safety run-in part, the following information (summaries and/or listings) will be provided as far as data is available:

- Number (%) of participants treated and included in the analysis sets
- Basic demographic and background data
- Disease characteristics (including cytogenetics, molecular genetics, and ELN risk category)
- Allogeneic transplant characteristics
- Medical history
- Prior and concomitant medications (including immunosuppressive therapy)
- Participant disposition
- Protocol deviations
- Duration of exposure to study treatment
- Dose intensity and relative dose intensity
- Number (%) of participants with any dose changes (incl. reductions, interruptions, or permanent discontinuations) and the reasons
- DLTs, AEs, treatment related AEs, SAEs, on-treatment deaths reported during the DLT evaluation period, as well as DLTs, AEs, treatment related AEs, SAEs, on-treatment deaths reported up to the data cut-off date
- AESI overview
- Posterior distribution for the risk of DLT for new participants at the dose level tested (see Section 2.5.2)
- Laboratory data and vital signs abnormalities
- Blast counts from bone marrow, peripheral blood (CBC and differential), extramedullary disease assessment and investigator's response assessment (if available)

- Siremadlin concentrations (if available)
- Antineoplastic therapies since discontinuation of study treatment (medication and cellular therapies)

For the regular safety review meetings, the same information as listed above will be provided

The exact list of tables, listings and figures prepared for those safety review meetings will be defined in a separate planning document.

3 Sample size calculation

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 Protocol 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 2.5.2), 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, 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 3-1 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 3-2 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.

4 Change to protocol specified analyses

As Novartis decided to permanently halt the enrollment of the study HDM201K12201 in September 2023, the following analyses as per protocol will not be performed:

- The primary safety analysis to determine RD for Part 2,
- The primary efficacy analysis of CR rate in Part 2,
- Secondary time-to-event endpoints for Part 1 RD and Part 2, including RFS, cumulative incidence of relapse, OS, and GRFS,
- [redacted]

5 Appendix

5.1 General definitions

End date of the last cycle

The end date of the last cycle is the maximum date between:

- The planned end date (Day 28 for Part 1, priming and maintenance phase of Part 2; 42 days of combination phase of Part 2) of the last cycle when the last non-zero dose of siremadlin) is administered,
- The actual date of the last administration of a non-zero dose of siremadlin.

The end date of the last cycle initiated will be applicable even if this date goes beyond the data cut-off date.

Date of last exposure to study treatment

One cycle planned length is 28 days for Part 1 and Part 2 (priming, maintenance), and one cycle planned length is 42 days for combination phase in Part 2. The start date of a cycle is defined as the first administration of siremadlin within a cycle. Siremadlin is planned to be administered QD D1-D5.

The date of last exposure to siremadlin is therefore calculated as:

- Minimum (date of last administration of siremadlin + 23 days, date of death, last contact date in case participant is lost to follow-up), as siremadlin is given QD D1-D5.

Date of last exposure and duration of exposure to study treatment combination

For the calculation of the duration of exposure to study treatment combination (siremadlin + DLI), the date of last exposure to study treatment combination will be derived as the minimum date between:

- End date of the last cycle,
- Date of death,
- Last contact date in case participant is lost to follow-up.

The duration of exposure to study treatment combination will be calculated as follow: date of last exposure to study treatment combination - date of first administration of study treatment combination + 1.

Duration from first to last cycle to calculate dose intensity and the relative dose intensity

For the calculation of the dose intensity and relative dose intensity, the duration in days from first to last cycle will be calculated as follows: end date of the last cycle - date of first administration of study treatment + 1.

Thus, this derivation will be irrespective of date of death or last contact date (i.e., it should not be truncated to the date of death or date of last contact date).

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

5.2 Laboratory parameters derivations

If laboratory values are provided as '<X' (i.e., below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

The following rules will be applied to derive the WBC differential percentages when only absolute differential counts are available for a xxx differential

xxx %value = (xxx count * 100) / WBC count

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, if only serum calcium is collected, the corrected calcium can be derived using the total serum calcium value and serum albumin at the same assessment using the following formula (after values had been converted to SI units):

Corrected Calcium (mmol/L) = Calcium (mmol/L) + 0.02 (40 – [Albumin (g/L)]

For laboratory CTC grade derivations, the normal range for derived corrected calcium is set to the same limits (in mmol/L) as for serum calcium.

6 Reference

References are available upon request

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