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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

HDM201/siremadlin

Trial Indication(s)

Acute myeloid leukemia (AML)

Protocol Number

CHDM201I12201

Protocol Title

A phase Ib/II open label dose confirmation, proof of concept study of siremadlin in combination with venetoclax plus azacitidine in unfit adult AML participants who responded sub-optimally to first-line venetoclax plus azacitidine treatment and in participants with newly diagnosed unfit AML presenting with high-risk clinical features

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase II

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Study Start/End Dates

Study Start Date: May 17, 2022 (Actual)
Primary Completion Date: April 17, 2024 (Actual)
Study Completion Date: April 17, 2024 (Actual)

Reason for Termination (If applicable)

Following the enrollment of 14 participants, Novartis decided to permanently halt recruitment and terminate the HDM201 program. This decision was not driven by any safety findings or safety concerns.

Study Design/Methodology

This was a Phase Ib/II, open-label, multi-center study of siremadlin in combination with venetoclax plus azacitidine in adult participants with AML who were ineligible for intensive chemotherapy, referred to as 'unfit AML participants´.

The study aimed to evaluate two sub-populations of adult participants with unfit AML in two separate arms. Arm 1 included participants who responded sub-optimally to first-line venetoclax plus azacitidine treatment, while Arm 2 included participants with newly diagnosed untreated AML presenting with high-risk (HR) clinical features (high-risk clinical features relates to factors conferring a low likelihood of response to venetoclax plus azacitidine). Participants were assigned to Arm 1, or Arm 2 based on their disease/treatment status, and both the arms were enrolled in parallel.

Siremadlin in combination with venetoclax plus azacitidine, was administered in cycles with a planned duration of 28 days for each cycle. The treatment continued until the participants experienced disease progression/relapse or unacceptable toxicity or reached end of Cycle 4 with response less than partial remission (PR). At the time of the termination decision, there were 28 participants screened, of which 14 participants were enrolled into the treatment phase (Arm 1 and Arm 2). The study was planned to be conducted in 2 parts.

Part 1 was the safety run-in part.

In Cohort 1 Arm 1, a total of 6 participants were enrolled and received treatment with siremadlin 20 mg QD Days 1-5 (28 Day cycle) in combination with venetoclax administered at 400 mg on each day of every cycle and azacitidine administered at 75mg/m^2 on days 1 to 7 of every cycle or alternatively on days 1 to 5 and then 8 to 9 of every

cycle. Three of these 6 participants met evaluability criteria to be included in the dose determining set based on current protocol amendment 3 with no Dose Limiting Toxicities (DLT) reported.

In Cohort 1 Arm 2, a total of 8 participants were enrolled 7 and received treatment (one participant was excluded due to TP53 mutation) with siremadlin 20 mg QD Days 1-5 (28 Day cycle) in combination with venetoclax 400 mg on each day of every cycle and azacitidine 75mg/m^2 on days 1 to 7 of every cycle or alternatively on days 1 to 5 and then 8 to 9 of every cycle. 7 of the 8 participants met evaluability criteria to be included in the dose determining set based on current protocol amendment 3 with one reported DLT

Part 2 was to be the Expansion part, aimed to further assess the efficacy and safety of siremadlin Recommended Dose for Expansion (RDE) in combination with venetoclax plus azacitidine. However, as Novartis decided to put enrollment in permanent halt and terminate the siremadlin program, RDE was not determined. Hence, the enrollment in Part 2 (Expansion phase) was not opened. This decision was not driven by any safety findings or safety concerns.

All participants were followed for 30 days after the last dose of study treatment to assess safety.

Centers

10 centers in 7 countries: Malaysia(2), Hungary(1), United States(2), Italy(1), Hong Kong(1), Turkey(1), Israel(2)

Objectives:

Primary objective(s):

Safety Run-in:

- To determine the recommended dose of siremadlin in combination with venetoclax plus azacitidine to be explored further in the expansion phase (RDE), separately in Arm 1 and Arm 2.
- To evaluate preliminary efficacy of siremadlin at the determined recommended dose for expansion (RDE) when administered in combination with venetoclax plus azacitidine in achieving Complete Remission (CR) (Arm 1 only).

Secondary objective(s):

- To characterize safety and tolerability profile of siremadlin when administered in combination with venetoclax plus azacitidine (Arms 1 and 2).
- To assess the CR rate (Arm 2 only; for Arm 1, assessment of CR is a primary endpoint).
- To assess the duration of CR in Arm 1 as well as in Arm 2.
- To assess the CR/CRh and CR/CRi rates with CRh defined as CR with partial hematological recovery (neutrophils > 0.5 $X10^9$/L and platelet > $50X10^9$/L) and CRi defined as CR with incomplete hematological recovery (neutrophils <$1.0X10^9$/L and/or platelets <$100X10^9$/L) (Arm 1 and 2).
- To assess the duration of CR/CRh and CR/Cri (Arm 1 and 2).
- To assess the Overall Survival (OS) (Arm 1 and 2).
- To assess early mortality, defined by 30- and 60- day mortality from the start of study treatment (Arm 1 and 2).
- To characterize the PK of siremadlin, venetoclax and azacitidine administered in combination (Arms 1 and 2).
- To assess the effect of siremadlin in combination with venetoclax plus azacitidine on measurable residual disease (MRD).

Test Product (s), Dose(s), and Mode(s) of Administration

Siremadlin (HDM201) was provided orally in the form of 10 mg, 20 mg and 30 mg (might have been included as an additional strength) capsules, venetoclax was provided orally in the form of 10 mg, 50 mg or 100 mg tablets or as per local supply, and azacitidine 100 mg (formulation provided as approved by local regulations) was provided as powder for suspension for injection, or powder for solution for subcutaneous injection or intravenous infusion.

Statistical Methods

Statistical analyses were performed by Novartis in accordance with the statistical analysis plan prepared by Novartis trial statisticians and using the most recent version of SAS (statistical analysis software) available in Novartis.

Analysis sets:

- Full Analysis Set (FAS): Comprises of all participants with no TP53 mutations confirmed by central laboratory that received any study drug (i.e. at least one dose of siremadlin or at least one dose of venetoclax or at least one dose azacitidine).

- Safety Set: The safety set includes all the participants that received any study drug (i.e., at least one dose of siremadlin or at least one dose of venetoclax or at least one dose of azacitidine).
- Dose-Determining Set (DDS): Comprises of all participants from the Safety Set in safety run-in who met the minimum exposure criterion and have sufficient safety evaluations or have experienced a DLT during Cycle 1.
- Pharmacokinetic Analysis Set (PAS): Includes all the participants in the Safety Set who provided at least one evaluable PK concentration of siremadlin, venetoclax, or azacitidine

Analysis of primary endpoint:

For the Safety run-in part, the primary endpoint was the incidence of DLTs between C1D1 and the end of Cycle 1 for participants in each cohort and incorporated in the DDS including participants whose TP53 mutational status cannot be confirmed by central laboratory.

The primary efficacy endpoint of the study (combining data from the Safety run-in part and the Expansion part for Arm 1 participants) was the proportion of evaluable participants (participants with no functional TP53 mutations by central laboratory) treated with siremadlin at RDE achieving CR as per investigator. As Novartis decided to permanently halt the enrollment, the RDE of Arm 1 was not determined and the Expansion part was not opened. The primary endpoint was not analyzed as per the plan, participants with CR was reported in Arm 1.

Analysis of Secondary Endpoint:

Efficacy:

No formal statistical tests were performed for any of the secondary efficacy endpoints.

CR rate (Arm 2 only), CR/CRh rate and CR/CRi rate:

CR rate was defined as the proportion of participants with best overall response of CR. CR/CRh rate was defined as the proportion of participants with best overall response of either CR or CRh. CR/CRi rate was defined as the proportion of participants with best overall response of either CR or CRi.

CR rate, CR/CRh rate and CR/CRi rate were provided with exact 95% CI.

Early mortality

Early mortality was defined as the proportion of participants who died from any cause within 30- and 60-day of starting treatment. This was calculated as the ratio of deaths to the total number of participants at Day 30 and Day 60. Results were presented by dose level and treatment arm, with exact 95% confidence intervals.

MRD negativity rate

MRD negativity rate was the proportion of participants with a CR/CRh/CRi who had an MRDnegative sample.
MRD negativity was defined as a frequency of Leukemia associated immunophenotype (LAIP) below 0.1%, determined by an MFC-AML MRD assay. The best MRD status was summarized descriptively with exact 95% confidence intervals overall in participants with a CR and in participants with composite CR (CR/CRh and CR/CRi).

Safety:

Safety analyses were performed using the Safety Set (regardless of confirmation of TP53 mutational status by central laboratory) by arm and dose level of siremadlin.

Safety summaries included only data from the on-treatment period with the exception of baseline data
The overall observation period was divided into three mutually exclusive segments:
1. Pre-treatment period: from day of participant's informed consent to the day before first administration of any study treatment.
2. On-treatment period: from date of first administration of any study treatment component to 30 days after date of last administration of any study treatment.
3. Post-treatment period: any observation starting at day 31 after last administration of any study treatment.

Summary tables for adverse events (AEs), serious adverse events (SAEs), deaths and adverse events of special interests (AESIs) were provided. Additionally, tables for laboratory data, ECG and cardiac imaging along with notable ECG values, vital signs along with notable vital sign values and demographics were provided.

Analysis of PK Endpoints: PK parameters for siremadlin, venetoclax and azacitidine were determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin Version 8.3 (Pharsight, Mountain View, CA).

Pharmacokinetic parameters were derived from the individual concentration versus time profile using a non-compartmental method as implemented in Phoenix WinNonlin.

Descriptive summary statistics for siremadlin, venetoclax and azacitidine concentrations were provided. All concentration vs. time profiles data for siremadlin, venetoclax and azacitidine were displayed graphically.

Sample size calculation: No formal statistical power calculations to determine sample size for safety run-in part (Arm 1 and Arm 2) were performed for this study.

For primary safety analysis, only participants in DDS were evaluable. For each arm, initially, at least 3 evaluable participants were treated at the starting dose (siremadlin 20 mg q.d) in combination with venetoclax plus azacitidine. In case of specific toxicities, the participating Investigators and Novartis study personnel could decide to increase the dose or expand at 20 mg q.d siremadlin. For a dose level to be considered for RDE, at least 6 evaluable participants were required.

For the Expansion part and Arm 1 Safety run-in at RDE sample size was calculated based on the CR rate for Arm 1 participants treated with siremadlin at the RDE from Arm 1 Safety run-in.

The Bayesian formulation of this dual criterion design is expressed as below:

- Clinical relevance: the posterior median of CR rate is ≥ 30% (decision value) and
- Statistical significance: the posterior probability that CR rate is ≥ 15% (null value) is at least 97.5%

With two criteria stated above the minimally required sample size (n_{min}) was 23, and the final sample size was set to 25 including participants treated at RDE from Arm 1 Safety run-in and the Expansion.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Age at the date of signing the informed consent form (ICF):

--Arm 1 and Arm 2: ≥ 18 years

- Participants diagnosed with AML based on WHO 2016 classification (Arber et al 2016) who are ineligible for standard induction chemotherapy and:
--Arm 1 : have received at least 2 cycles and not more than 4 cycles of first-line venetoclax plus azacitidine treatment and have not achieved a CR, CRi, CRh or MLFS.
--Arm 2 : newly diagnosed AML with adverse genetic risk stratification (according to ELN 2022) (except TP53 mutation positive participants).
- Participant (in both arms) must be considered ineligible for standard of care intensive induction chemotherapy defined by the following:
≥ 75 years of age;
OR
≥ 18 to 74 years of age with at least one of the following co-morbidities:
Eastern Cooperative Oncology Group (ECOG) Performance Status of 2 or 3;
Cardiac history of congestive heart failure (CHF) requiring treatment or Ejection Fraction ≤ 50% or chronic stable angina;
DLCO ≤ 65% or FEV1 ≤ 65%.
- Participants must have an ECOG performance status:
0 to 2 for participants ≥ 75 years of age.
OR
0 to 3 for participants ≥ 18 to 74 years of age.
- WBC < 25x109/L
- AST and ALT ≤ 3 × ULN
- Estimated Glomerular Filtration Rate (eGFR)≥ 60 mL/min/1.73 m2

Exclusion Criteria:

- Prior exposure to MDM2-inhibitor therapy at any time.
- Participants with TP53 mutation positive.
- Participants with del17p.
- Participants with AML-M3 / APL (Acute promyelocytic leukemia) with PML-RARA (Promyelocytic leukemia/retinoic acid receptor alpha) or with AML secondary to Down's syndrome.
- Participants treated with FLT3 inhibitors for AML indication are not eligible.
- Participants who require treatment with moderate or strong CYP3A4 inducers within 14 days prior to starting study treatment, or are expected to receive moderate or strong CYP3A4 inducers during the entire study
- Participants who require treatment with substrates of CYP3A4/5 with a narrow therapeutic index.

Participant Flow Table

Overall Study

	Arm 1: Adult participants with unfit AML	Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features	Total
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	

Started	6	8	14
Did not enter post-treatment follow-up	4	6	10
Entered post-treatment follow-up, discontinued	2	1	3
Safety Set	6	8	14
Full Analysis Set (FAS)	6	7	13
Excluded from FAS due to TP53	0	1	1
Completed	0	0	0
Not Completed	6	8	14
Death	3	7	10
Study Terminated by Sponsor	2	0	2
Subject Decision	1	0	1
Excluded from FAS due to TP53 & died	0	1	1

Baseline Characteristics

	Arm 1: Adult participants with unfit AML	**Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features**	**Total**
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to	

	Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	
Number of Participants [units: participants]	6	8	14
Baseline Analysis Population Description	The Safety Set includes all participants that received any study treatment component (i.e., at least one dose of siremadlin or at least one dose of venetoclax or at least one dose azacitidine		
Age, Customized (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
< 65 years	1	0	1
>= 65 years	5	8	13
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	4	3	7
Male	2	5	7
Race/Ethnicity, Customized (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			

White	6	4	10
Asian	0	4	4

Primary Outcome Result(s)

Percentage of participants with Dose Limiting Toxicities (DLTs) as per investigator assessment reported during the first cycle (Part 1: Safety run-in part)

Description	A dose-limiting toxicity (DLT) is defined as an adverse event (AE) or abnormal laboratory value considered by the Investigator to be at least possibly related to siremadlin as a single contributor or in combination with other component(s) of study treatment that occurs beginning the first day of siremadlin dosing in the study until end of cycle 1.
Time Frame	From Cycle 1 Day 1 to Cycle 1 Day 28; Cycle = 28 days
Analysis Population Description	Dose-Determining Set (DDS): Comprises of all participants from the Safety Set in safety run-in who met the minimum exposure criterion and have sufficient safety evaluations or have experienced a DLT during Cycle 1.

	Arm 1: Adult participants with unfit AML	Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.

Number of Participants Analyzed [units: participants]	3	7
Percentage of participants with Dose Limiting Toxicities (DLTs) as per investigator assessment reported during the first cycle (Part 1: Safety run-in part) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	0 (%)	1 (14.29%)

Percentage of participants achieving a complete remission (CR) rate as per investigator assessment (Arm 1 only: Safety run-in part)

Description	Assessed by CR rate. CR rate is defined as the percentage of participants with best overall response of complete remission (CR) as per investigator assessment using the international guidelines for assessment of response in AML (IWG ELN criteria 2027 and 2022).
Time Frame	Day 14, Day 28, Day 56 and then every 84 days; end of treatment; estimated median time on follow-up was 57 days
Analysis Population Description	Full Analysis Set (FAS) comprises of all participants in Arm 1 with no TP53 mutations confirmed by central laboratory that received any study drug (i.e. at least one dose of siremadlin or at least one dose of venetoclax or at least one dose azacitidine).

	Arm 1: Adult participants with unfit AML
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	6
Percentage of participants achieving a complete remission (CR) rate as per investigator assessment (Arm 1 only: Safety run-in part) (units: Participants)	**Count of Participants (Not Applicable)**
	1 (16.67%)

Secondary Outcome Result(s)

Percentage of participants achieving complete remission (CR) as per Investigator assessment - Arm 2 only (Part 1: Safety run-in part)

Description	Assessed by CR rate. CR rate is defined as the percentage of participants with best overall response of complete remission (CR) as per investigator assessment using the international guidelines for assessment of response in AML (IWG ELN criteria 2027 and 2022).
Time Frame	Day 14, Day 28, Day 56 and then every 84 days; end of treatment; estimated median time on follow-up was 66 days
Analysis Population Description	Full Analysis Set (FAS) comprises of all participants in Arm 2 with no TP53 mutations confirmed by central laboratory that received any study drug (i.e. at least one dose of siremadlin or at least one dose of venetoclax or at least one dose azacitidine).

	Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features
Arm/Group Description	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	7
Percentage of participants achieving complete remission (CR) as per Investigator assessment - Arm 2 only (Part 1: Safety run-in part) (units: Participants)	**Count of Participants (Not Applicable)**
	0 (%)

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Time from date of the first documented CR to the date of the first documented relapse or death due to any cause, whichever occurs first (Part 2: Expansion phase)

Description	Duration of CR is defined as time from the date of the first documented CR to the date of first documented relapse or death due to any cause, whichever occurs first. Assessment of duration of CR in participants who achieved a CR. This endpoint was not analyzed because Part 2 was not conducted.
Time Frame	Day 14, Day 28, Day 56 and then every 84 days; end of treatment
Analysis Population Description	Full Analysis Set (FAS) comprises of all participants in Arm 2 with no TP53 mutations confirmed by central laboratory that received any study drug (i.e. at least one dose of siremadlin or at least one dose of venetoclax or at least one dose azacitidine). This endpoint was not analyzed because Part 2 was not conducted.

	Arm 1: Adult participants with unfit AML	Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	0	0
Time from date of the first documented CR to the date of the first documented relapse or death due to any cause, whichever occurs first (Part 2: Expansion phase) (units:)	**()**	**()**

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Percentage of participants achieving CR or complete remission with partial hematological recovery (CRh) (Part 1: Safety run-in part)

Description	Assessed by CR/CRh rate. CR/CRh rate is defined as the percentage of participants with best overall response of either complete remission or complete remission with partial hematological recovery (CR/CRh) as per investigator assessment using the international guidelines for assessment of response in AML (IWG ELN criteria 2027 and 2022).
Time Frame	Day 14, Day 28, Day 56 and then every 84 days; end of treatment; estimated median time on follow-up was 57 days for Arm 1; estimated median time on follow-up was 66 days for Arm 2
Analysis Population Description	Full Analysis Set (FAS) comprises of all participants with no TP53 mutations confirmed by central laboratory that received any study drug (i.e. at least one dose of siremadlin or at least one dose of venetoclax or at least one dose azacitidine).

	Arm 1: Adult participants with unfit AML	**Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features**
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	6	7
Percentage of participants achieving CR or complete remission with partial hematological recovery (CRh) (Part 1: Safety run-in part) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	1 (16.67%)	3 (42.86%)

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Percentage of participants achieving complete remission (CR) or complete remission with incomplete hematological recovery (CRi) (Part 1: Safety run-in part)

Description	Assessed by CR/CRi rate. CR/CRi rate is defined as the percentage of participants with best overall response of either complete remission or complete remission with incomplete hematological recovery (CR/CRi) as per investigator assessment using the international guidelines for assessment of response in AML (IWG ELN criteria 2027 and 2022).
Time Frame	Day 14, Day 28, Day 56 and then every 84 days; end of treatment; estimated median time on follow-up was 57 days for Arm 1; estimated median time on follow-up was 66 days for Arm 2
Analysis Population Description	Full Analysis Set (FAS) comprises of all participants with no TP53 mutations confirmed by central laboratory that received any study drug (i.e. at least one dose of siremadlin or at least one dose of venetoclax or at least one dose azacitidine).

	Arm 1: Adult participants with unfit AML	**Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features**
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	6	7
Percentage of participants achieving complete remission (CR) or complete remission with incomplete hematological recovery (CRi) (Part 1: Safety run-in part) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**

	1 (16.67%)	1 (14.29%)

Time from the date of the first documented CR/CRh to the date of first documented relapse or death due to any cause, whichever occurs first (Part 2: Expansion phase)

Description	Assessed by duration of CR/CRh. Duration of CR/CRh is defined as time from the date of the first documented CR/CRh to the date of first documented relapse or death due to any cause, whichever occurs first. This endpoint was not analyzed because Part 2 was not conducted.
Time Frame	Day 14, Day 28, Day 56 and then every 84 days; end of treatment
Analysis Population Description	Full Analysis Set (FAS) comprises of all participants with no TP53 mutations confirmed by central laboratory that received any study drug (i.e. at least one dose of siremadlin or at least one dose of venetoclax or at least one dose azacitidine). This endpoint was not analyzed because Part 2 was not conducted.

	Arm 1: Adult participants with unfit AML	**Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features**
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	0	0
Time from the date of the first documented CR/CRh to the date of first documented relapse or death due to any cause, whichever occurs first (Part 2: Expansion phase) (units:)	**()**	**()**

Time from the date of the first documented CR/CRi to the date of first documented relapse or death due to any cause, whichever occurs first (Part 2: Expansion phase)

Description	Assessed by duration of CR/CRi. Duration of CR/CRi is defined as time from the date of the first documented CR/CRi to the date of first documented relapse or death due to any cause, whichever occurs first. This endpoint was not analyzed because Part 2 was not conducted.
Time Frame	Day 14, Day 28, Day 56 and then every 84 days; end of treatment
Analysis Population Description	Full Analysis Set (FAS) comprises of all participants with no TP53 mutations confirmed by central laboratory that received any study drug (i.e. at least one dose of siremadlin or at least one dose of venetoclax or at least one dose azacitidine). This endpoint was not analyzed because Part 2 was not conducted.

	Arm 1: Adult participants with unfit AML	Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	0	0
Time from the date of the first documented CR/CRi to the date of first documented relapse or death due to any cause, whichever occurs first (Part 2: Expansion phase) (units:)	()	()

Overall Survival (OS) (Part 1: Safety run-in part and Part 2: Expansion phase)

Description	OS is the time from start of treatment to death due to any cause.
Time Frame	Every 3 months after end of treatment. Estimated median survival follow-up: 186 Days for Arm 1 (part 1), 91 Days for Arm 2 (Part 1)
Analysis Population Description	Full Analysis Set comprised all participants with no TP53 mutations confirmed by central laboratory who received any study drug (i.e. at least one dose of siremadlin or at least one dose of venetoclax or at least one dose azacitidine). The enrollment in Part 2 (expansion phase) was not opened because of program termination. Since the Recommended Dose for Expansion (RDE) was not determined for either arm, this analysis that required RDE was not performed for Part 1 and Part 2.

	Arm 1: Adult participants with unfit AML	Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	0	0
Overall Survival (OS) (Part 1: Safety run-in part and Part 2: Expansion phase) (units:)	()	()

Early mortality (Arm 1 & 2 in Part 1: Safety run-in part)

Description	Early mortality was defined as the percentage of participants who died from any cause within 30- and 60-day of starting treatment. This was calculated as the ratio of deaths to the total number of participants at Day 30 and Day 60.
Time Frame	30 days & 60 days from start of study treatment
Analysis Population Description	Full Analysis Set (FAS) comprises of all participants with no TP53 mutations confirmed by central laboratory that received any study drug (i.e. at least one dose of siremadlin or at least one dose of venetoclax or at least one dose azacitidine).

	Arm 1: Adult participants with unfit AML	**Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features**
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	6	7
Early mortality (Arm 1 & 2 in Part 1: Safety run-in part) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Death in first 30 days from treatment start	0 (%)	1 (14.29%)
Death in first 60 days from treatment start	2 (33.33%)	2 (28.57%)

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Pharmacokinetic (PK) parameters: AUC0-24h and AUClast of siremadlin and venetoclax (Part 1: Safety run-in part)

Description	AUC0-24h: The area under the concentration vs. time Curve (AUC) from time zero to specified time point: 24h. AUClast is the AUC from time zero to the last quantifiable concentration point (last) (mass x time x volume -1).
Time Frame	Pre-dose, 0.5 hour (h), 1h, 2h, 3h, 6h, 8h and 12h, 24h post-dose, Days 1 & 5 of Cycles 1 & 5; Cycle = 28 Days
Analysis Population Description	Pharmacokinetic Analysis Set (PAS): Includes all the participants in the Safety Set who provided at least one evaluable PK concentration of siremadlin, venetoclax, or azacitidine.

	Arm 1: Adult participants with unfit AML	**Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features**
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	6	8
Pharmacokinetic (PK) parameters: AUC0-24h and AUClast of siremadlin and venetoclax (Part 1: Safety run-in part) (units: h*ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
AUC0-24h: Siremadlin Cycle (C)1 Day (D)1	2542 (52.9%)	2626 (34.8%)
AUC0-24h: Siremadlin C1D5	2223 (28.4%)	3556 (74.7%)
AUC0-24h: Siremadlin C5D1 (n = 1, 1)	6405	1689

AUC0-24h: Siremadlin C5D5 (n = 0, 1)		1466
AUClast: Siremadlin C1D1	2555 (52.6%)	2636 (34.4%)
AUClast: Siremadlin C1D5	2226 (28.3%)	3569 (74.4%)
AUClast: Siremadlin C5D1 (n = 1, 1)	6602	1755
AUClast: Siremadlin C5D5 (n = 0, 1)		1495
AUC0-24h: Venetoclax C1D1 (n = 5, 6)	11165 (114.1%)	7792 (91.7%)
AUC0-24h: Venetoclax C1D5 (n = 4, 3)	15913 (164.6%)	60251 (62.3%)
AUC0-24h: Venetoclax C5D1(n = 1, 1)	44472	6503
AUClast: Venetoclax C1D1 (n = 5 ,8)	11207 (111.5%)	6602 (103.5%)
AUClast: Venetoclax C1D5 (n = 5, 7)	17738 (136.2%)	55722 (48.2%)
AUClast: Venetoclax C5D1 (n = 1, 1)	43942	6557
AUClast: Venetoclax C5D5 (n = 0, 1)		50109

Pharmacokinetic (PK) parameters: AUC of azacitidine (Part 1: Safety run-in part)

Description	AUC0-3h and 6h: The area under the concentration vs. time Curve (AUC) from time zero to specified time point.
Time Frame	Cycle 1 and 5 at Day 1 pre-dose, 0.5 h, 1 h, 2 h, 3 h, 6 h; Cycle = 28 Days
Analysis Population Description	Pharmacokinetic Analysis Set (PAS): Includes all the participants in the Safety Set who provided at least one evaluable PK concentration of siremadlin, venetoclax, or azacitidine.

	Arm 1: Adult participants with unfit AML	**Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features**
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus

	of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	4	8
Pharmacokinetic (PK) parameters: AUC of azacitidine (Part 1: Safety run-in part) (units: h*ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
AUC0-3h: C1D1(n = 3, 8)	1162 (79.0%)	621 (155.0%)
AUC0-3h: C5D1 (n = 0, 1)		694
AUC0-6h: C1D1 (n = 3, 6)	1302 (69.2%)	1042 (39.1%)
AUC0-6h: C5D1 (n = 0, 1),		951
AUClast: C1D1 (n = 4, 8)	979 (83.2%)	587 (179.5%)
AUClast: C5D1 (n = 0, 1)		951

PK parameter: Cmax of siremadlin and venetoclax (Part 1: Safety run-in part)

Description	Cmax is the maximum (peak) observed plasma, blood, serum or other body fluid drug concentration following drug administration (mass x volume -1)
Time Frame	Pre-dose, 0.5 hour (h), 1h, 2h, 3h, 6h, 8h and 12h, 24h post-dose, Days 1 & 5 of Cycles 1 & 5; Cycle = 28 Days
Analysis Population Description	Pharmacokinetic Analysis Set (PAS): Includes all the participants in the Safety Set who provided at least one evaluable PK concentration of siremadlin, venetoclax, or azacitidine for this endpoint.

	Arm 1: Adult participants with unfit AML	**Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features**

Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	6	8
PK parameter: Cmax of siremadlin and venetoclax (Part 1: Safety run-in part) (units: ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
Siremadlin: C1D1	179 (62.6%)	177 (35.6%)
Siremadlin: C1D5	163 (30.8%)	229 (67.5%)
Siremadlin: C5D1 (n = 1, 1)	397	100
Siremadlin: C5D5 (n = 0, 1)		80
Venetoclax: C1D1 (n = 5, 8)	923 (82.6%)	441 (129.8%)
Venetoclax: C1D5 (n = 5, 7)	1181 (98.6%)	3387 (40.0%)
Venetoclax: C5D1 (n = 1, 1)	2900	358
Venetoclax: C5D5 (n = 0, 1)		2840

PK parameter: Cmax of azacitidine (Part 1: Safety run-in part)

Description	Cmax is the maximum (peak) observed plasma, blood, serum or other body fluid drug concentration following drug administration (mass x volume -1)
Time Frame	Cycle 1 and 5 at Day 1 pre-dose, 0.5 h, 1 h, 2 h, 3 h, 6 h; Cycle = 28 Days

Analysis Population Description	Participants in the PAS with an available value for the outcome measure. Pharmacokinetic Analysis Set (PAS): Includes all the participants in the Safety Set who provided at least one evaluable PK concentration of azacitidine for this endpoint.

	Arm 1: Adult participants with unfit AML	Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	4	8
PK parameter: Cmax of azacitidine (Part 1: Safety run-in part) (units: ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
C1D1 (n = 4, 8)	787 (70.2%)	543 (114.9%)
C5D1 (n = 0, 1)		541

PK parameter: Tmax of siremadlin and venetoclax (Part 1: Safety run-in part)

Description	Tmax is the time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after drug administration (time). Actual sampling times were taken into consideration for the calculation of Tmax.
Time Frame	Pre-dose, 0.5 hour (h), 1h, 2h, 3h, 6h, 8h and 12h, 24h post-dose, Days 1 & 5 of Cycles 1 & 5; Cycle = 28 Days

Analysis Population Description	Participants in the PAS with an available value for the outcome measure. Pharmacokinetic Analysis Set (PAS): Includes all the participants in the Safety Set who provided at least one evaluable PK concentration of siremadlin, venetoclax, or azacitidine for this endpoint.

	Arm 1: Adult participants with unfit AML	**Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features**
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	6	8
PK parameter: Tmax of siremadlin and venetoclax (Part 1: Safety run-in part) (units: hours)	**Median (Full Range)**	**Median (Full Range)**
Siremadlin: C1D1	4.46 (2.0 to 24.0)	2.70 (1.1 to 24.0)
Siremadlin: C1D5	3.08 (2.1 to 12.0)	2.0 (1.0 to 5.9)
Siremadlin: C5D1 (n = 1, 1)	24.5 (24.5 to 24.5)	2.0 (2.0 to 2.0)
Siremadlin: C5D5 (n = 0, 1)		2.0 (2.0 to 2.0)
Venetoclax: C1D1 (n = 5, 8)	6.0 (5.9 to 25.1)	7.0 (5.8 to 24.0)

Venetoclax: C1D5 (n = 5, 7)	6.0 (3.0 to 23.1)	7.92 (6.0 to 12.0)
Venetoclax: C5D1(n = 1, 1)	6.0 (6.0 to 6.0)	7.5 (7.5 to 7.5)
Venetoclax: C5D5(n = 0, 1)		10.0 (10.0 to 10.0)

PK parameter: Tmax of azactidine (Part 1 (Safety run-in))

Description	Tmax is the time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after drug administration (time). Actual sampling times were taken into consideration for the calculation of Tmax.
Time Frame	Cycle 1 and 5 at Day 1 pre-dose, 0.5 h, 1 h, 2 h, 3 h, 6 h; Cycle = 28 Days
Analysis Population Description	Participants in the PAS with an available value for the outcome measure. Pharmacokinetic Analysis Set (PAS): Includes all the participants in the Safety Set who provided at least one evaluable PK concentration of azacitidine.

	Arm 1: Adult participants with unfit AML	**Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features**
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	4	8

PK parameter: Tmax of azactidine (Part 1 (Safety run-in)) (units: hours)	**Median (Full Range)**	**Median (Full Range)**
C1D1	0.62 (0.4 to 1.0)	0.5 (0.3 to 2.0)
C5D1 (n = 0, 1)		0.5 (0.5 to 0.5)

Percentage of CR- Measurable Residual Disease (MRD) negative overall and in participants achieving a CR, CR/CRh, and CR/CRi (Part 1: Safety run-in part)

Description	Assessed by MRD-negativity rate. MRD negativity is defined as an MRD negative sample (frequency of LAIP below 0.1%, as determined by an MFC-AML MRD) assay at Central Lab) in participants with a CR, CRh or CRi as per investigator assessment.
Time Frame	At Screening, Cycle 1 Day 14, Cycle 2 Day 1, end of treatment, every 3 cycles until disease progression; estimated median time on follow-up was 57 days for Arm 1; estimated median time on follow-up was 66 days for Arm 2; Cycle = 28 Days
Analysis Population Description	Full Analysis Set (FAS) comprises of all participants with no TP53 mutations confirmed by central laboratory that received any study drug (i.e. at least one dose of siremadlin or at least one dose of venetoclax or at least one dose azacitidine).

	Arm 1: Adult participants with unfit AML	**Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features**
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.

Number of Participants Analyzed [units: participants]	6	7
Percentage of CR- Measurable Residual Disease (MRD) negative overall and in participants achieving a CR, CR/CRh, and CR/CRi (Part 1: Safety run-in part) (units: Percentage of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
	0.0 (0.0 to 45.9)	0.0 (0.0 to 41.0)

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

All Collected Deaths

Description	Adverse events and on-treatment deaths were collected from the first dose of study treatment until 30 days after last administration of study treatment, for a maximum duration of 7.3 months. Post-treatment survival follow-up deaths were collected 31 days after last dose of study medication until the end of the study, up to approx. 23 months.
Time Frame	AEs & On-treatment deaths: Up to approx. 7.3 months, Post-treatment survival follow-up deaths: Up to approx. 23 months after the end of treatment
Analysis Population Description	Clinical database population: all treated participants and participants who died in the post-treatment follow-up period of the study.

	Arm 1: Adult participants with unfit AML	**Arm 2: Adult participants with newly diagnosed unfit AML with high-risk clinical features**
Arm/Group Description	Adult participants with unfit AML who responded sub-optimally to at least 2 and not more than 4 cycles of first-line venetoclax plus azacitidine therapy. Siremadlin was administered at a dose	Adult participants with unfit AML who were newly diagnosed and presenting with high-risk clinical features (which related to factors conferring to a low likelihood of response to venetoclax plus

	of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.	azacitidine) and with adverse genetic risk stratification (according to ELN 2022) (Except TP53 mutation positive participants). Siremadlin was administered at a dose of 20 mg QD which could be increased based on toxicities; venetoclax was administered at 400 mg once daily and azacitidine was administered at 75 mg/m^2.
Number of Participants Analyzed [units: participants]	6	8
All Collected Deaths (units: Participants)		
Total Deaths	3	8
On-treatment deaths	1	4
Post-treatment deaths	2	4

Safety Results

Time Frame	Adverse Events (AEs) were collected from first dosing (Day 1) until 30 days after the date of last actual administration of study treatment, maximum treatment duration: approx. 9.3 months for Arm 1 and approx. 7.4 months for Arm 2.
Additional Description	An Adverse Event (AE) is any untoward medical occurrence 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.
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Arm 1: Adult participants with unfit AML (On-treatment) N = 6	Arm 2: Adult parts. with newly diagnosed unfit AML with high-risk clinical features (On-treatment) N = 8	Arm 1: Adult participants with unfit AML (Post-treatment survival follow-up (f/u)) N = 5	Arm 2: Adult parts. with newly diag. unfit AML with high-risk clin. features (Post-trtmnt surv. f/u) N = 4
Arm/Group Description	On-treatment period: from first dose of study treatment up to 30 days post-treatment.	On-treatment period: from first dose of study treatment up to 30 days post-treatment.	Deaths collected in the post- treatment survival follow-up phase (starting from day 31 post-treatment). No AEs were collected during this period	Deaths collected in the post- treatment survival follow-up phase (starting from day 31 post-treatment). No AEs were collected during this period
Total Number Affected	1	4	2	4
Total Number At Risk	6	8	5	4

Serious Adverse Events

Time Frame	Adverse Events (AEs) were collected from first dosing (Day 1) until 30 days after the date of last actual administration of study treatment, maximum treatment duration: approx. 9.3 months for Arm 1 and approx. 7.4 months for Arm 2.
Additional Description	An Adverse Event (AE) is any untoward medical occurrence 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.
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

	Arm 1: Adult participants with unfit AML (On-treatment) N = 6	Arm 2: Adult parts. with newly diagnosed unfit AML with high-risk clinical features (On-treatment) N = 8	Arm 1: Adult participants with unfit AML (Post-treatment survival follow-up (f/u)) N = 0	Arm 2: Adult parts. with newly diag. unfit AML with high-risk clin. features (Post-trtmnt surv. f/u) N = 0
Arm/Group Description	On-treatment period: from first dose of study treatment up to 30 days post-treatment.	On-treatment period: from first dose of study treatment up to 30 days post-treatment.	Deaths collected in the post- treatment survival follow-up phase (starting from day 31 post-treatment). No AEs were collected during this period	Deaths collected in the post- treatment survival follow-up phase (starting from day 31 post-treatment). No AEs were collected during this period
Total # Affected by any Serious Adverse Event	6	7	0	0
Total # at Risk by any Serious Adverse Event	6	8	0	0
Blood and lymphatic system disorders				
Febrile neutropenia	2 (33.33%)	3 (37.50%)		
Neutropenia	1 (16.67%)	1 (12.50%)		
Gastrointestinal disorders				
Diarrhoea	0 (0.00%)	1 (12.50%)		
Nausea	1 (16.67%)	0 (0.00%)		
Proctalgia	1 (16.67%)	0 (0.00%)		
Vomiting	1 (16.67%)	0 (0.00%)		
General disorders and administration site conditions				
Mucosal inflammation	0 (0.00%)	1 (12.50%)		

Pyrexia	1 (16.67%)	0 (0.00%)
Infections and infestations		
COVID-19	1 (16.67%)	0 (0.00%)
Enterococcal sepsis	1 (16.67%)	0 (0.00%)
Lower respiratory tract infection	0 (0.00%)	1 (12.50%)
Neutropenic sepsis	0 (0.00%)	2 (25.00%)
Sepsis	0 (0.00%)	2 (25.00%)
Septic shock	0 (0.00%)	2 (25.00%)
Soft tissue infection	1 (16.67%)	0 (0.00%)
Vascular device infection	0 (0.00%)	1 (12.50%)
Injury, poisoning and procedural complications		
Allergic transfusion reaction	1 (16.67%)	0 (0.00%)
Femoral neck fracture	1 (16.67%)	0 (0.00%)

Other (Not Including Serious) Adverse Events

Time Frame	Adverse Events (AEs) were collected from first dosing (Day 1) until 30 days after the date of last actual administration of study treatment, maximum treatment duration: approx. 9.3 months for Arm 1 and approx. 7.4 months for Arm 2.
Additional Description	An Adverse Event (AE) is any untoward medical occurrence 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.

Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Arm 1: Adult participants with unfit AML (On-treatment) N = 6	**Arm 2: Adult parts. with newly diagnosed unfit AML with high-risk clinical features (On-treatment) N = 8**	**Arm 1: Adult participants with unfit AML (Post-treatment survival follow-up (f/u)) N = 0**	**Arm 2: Adult parts. with newly diag. unfit AML with high-risk clin. features (Post-trtmnt surv. f/u) N = 0**
Arm/Group Description	On-treatment period: from first dose of study treatment up to 30 days post-treatment.	On-treatment period: from first dose of study treatment up to 30 days post-treatment.	Deaths collected in the post- treatment survival follow-up phase (starting from day 31 post-treatment). No AEs were collected during this period	Deaths collected in the post- treatment survival follow-up phase (starting from day 31 post-treatment). No AEs were collected during this period
Total # Affected by any Other Adverse Event	5	8	0	0
Total # at Risk by any Other Adverse Event	6	8	0	0
Blood and lymphatic system disorders				
Anaemia	2 (33.33%)	3 (37.50%)		
Cytopenia	0 (0.00%)	1 (12.50%)		
Febrile neutropenia	0 (0.00%)	2 (25.00%)		

Leukopenia	1 (16.67%)	2 (25.00%)
Neutropenia	2 (33.33%)	5 (62.50%)
Pancytopenia	0 (0.00%)	2 (25.00%)
Thrombocytopenia	1 (16.67%)	6 (75.00%)
Cardiac disorders		
Bundle branch block left	1 (16.67%)	0 (0.00%)
Palpitations	0 (0.00%)	1 (12.50%)
Supraventricular tachycardia	1 (16.67%)	0 (0.00%)
Eye disorders		
Retinal haemorrhage	0 (0.00%)	1 (12.50%)
Gastrointestinal disorders		
Abdominal pain	1 (16.67%)	0 (0.00%)
Anal fistula	0 (0.00%)	1 (12.50%)
Anal haemorrhage	0 (0.00%)	1 (12.50%)
Aphthous ulcer	1 (16.67%)	0 (0.00%)
Constipation	0 (0.00%)	1 (12.50%)
Diarrhoea	3 (50.00%)	2 (25.00%)
Flatulence	1 (16.67%)	0 (0.00%)
Nausea	3 (50.00%)	3 (37.50%)
Oesophageal spasm	1 (16.67%)	0 (0.00%)
Paraesthesia oral	0 (0.00%)	1 (12.50%)
Vomiting	1 (16.67%)	3 (37.50%)

General disorders and administration site conditions		
Asthenia	2 (33.33%)	2 (25.00%)
Chills	1 (16.67%)	0 (0.00%)
Fat necrosis	0 (0.00%)	1 (12.50%)
Fatigue	1 (16.67%)	1 (12.50%)
Injection site pain	1 (16.67%)	0 (0.00%)
Mucosal inflammation	0 (0.00%)	1 (12.50%)
Oedema peripheral	1 (16.67%)	0 (0.00%)
Pyrexia	0 (0.00%)	2 (25.00%)
Immune system disorders		
Hypersensitivity	0 (0.00%)	1 (12.50%)
Infections and infestations		
Conjunctivitis	1 (16.67%)	0 (0.00%)
COVID-19	0 (0.00%)	1 (12.50%)
Enterococcal bacteraemia	0 (0.00%)	1 (12.50%)
Pneumonia fungal	1 (16.67%)	0 (0.00%)
Respiratory syncytial virus infection	1 (16.67%)	0 (0.00%)
Sinusitis fungal	0 (0.00%)	1 (12.50%)
Urinary tract infection	0 (0.00%)	1 (12.50%)
Injury, poisoning and procedural complications		
Jaw fracture	1 (16.67%)	0 (0.00%)

Lip injury	1 (16.67%)	0 (0.00%)
Skin laceration	1 (16.67%)	0 (0.00%)
Investigations		
Alanine aminotransferase increased	1 (16.67%)	0 (0.00%)
Antithrombin III decreased	0 (0.00%)	1 (12.50%)
Aspartate aminotransferase increased	1 (16.67%)	0 (0.00%)
Blood bilirubin increased	1 (16.67%)	0 (0.00%)
C-reactive protein increased	0 (0.00%)	1 (12.50%)
Enterococcus test positive	0 (0.00%)	1 (12.50%)
International normalised ratio increased	1 (16.67%)	0 (0.00%)
Oxygen saturation decreased	1 (16.67%)	0 (0.00%)
Platelet count decreased	1 (16.67%)	1 (12.50%)
SARS-CoV-2 test positive	0 (0.00%)	1 (12.50%)
Weight decreased	0 (0.00%)	2 (25.00%)
White blood cell count decreased	1 (16.67%)	1 (12.50%)
Metabolism and nutrition disorders		
Decreased appetite	2 (33.33%)	0 (0.00%)
Hyperphosphataemia	1 (16.67%)	0 (0.00%)
Hypoalbuminaemia	0 (0.00%)	2 (25.00%)
Hypokalaemia	1 (16.67%)	4 (50.00%)
Hypomagnesaemia	0 (0.00%)	1 (12.50%)
Hypophosphataemia	0 (0.00%)	1 (12.50%)

Musculoskeletal and connective tissue disorders		
Pain in extremity	0 (0.00%)	1 (12.50%)
Nervous system disorders		
Dizziness	1 (16.67%)	0 (0.00%)
Headache	1 (16.67%)	1 (12.50%)
Syncope	1 (16.67%)	0 (0.00%)
Psychiatric disorders		
Anxiety	0 (0.00%)	1 (12.50%)
Confusional state	1 (16.67%)	0 (0.00%)
Delirium	0 (0.00%)	1 (12.50%)
Renal and urinary disorders		
Haematuria	0 (0.00%)	1 (12.50%)
Skin and subcutaneous tissue disorders		
Ecchymosis	1 (16.67%)	0 (0.00%)
Erythema	1 (16.67%)	1 (12.50%)
Purpura	0 (0.00%)	1 (12.50%)
Rash	0 (0.00%)	1 (12.50%)
Urticaria	0 (0.00%)	1 (12.50%)
Vascular disorders		
Subclavian vein occlusion	1 (16.67%)	0 (0.00%)
Thrombophlebitis	0 (0.00%)	1 (12.50%)

Other Relevant Findings

Not Applicable

Conclusion:

This Phase Ib/II, open-label, multi-center study evaluated siremadlin with venetoclax plus azacitidine in unfit adult AML participants. Two subpopulations were assessed:

- **Arm 1:** Participants with sub-optimal response to first-line venetoclax plus azacitidine (6 participants).
- **Arm 2:** Newly diagnosed, untreated AML participants with high-risk clinical features (8 participants).

The primary endpoints could not be evaluated since the study was early terminated and decision was not based on safety concerns. No new safety signals emerged from the study.

Date of Clinical Trial Report

CSR Published Date: 23 October 2024