Clinical trial results:
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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points and zeros where there is no data to report in this record are not an accurate representation of the clinical trial results.
Please use https://www.novctrd.com for complete rial results.

Summary

EudraCT number	2021-001165-21
Trial protocol	HU IT ES DE
Global end of trial date	17 April 2024

Results information

Result version number	v1 (current)
This version publication date	01 May 2025
First version publication date	01 May 2025

Trial information

Trial identification

Sponsor protocol code	CHDM201I12201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05155709
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novatis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novatis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 April 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaraion of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 May 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Türkiye: 1
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	14
EEA total number of subjects	3

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 10 sites in 7 countries. The study aimed to evaluate two sub-populations of adult participants with unfit AML in two separate arms: participants who responded sub-optimally to first-line venetoclax plus azacitidine treatment & participants with newly diagnosed untreated AML presenting with high-risk clinical features.

Pre-assignment

Screening details:

28 participants were screened in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1: Adult participants with unfit AML

Arm 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.

Arm type	Experimental
Investigational medicinal product name	Siremadlin
Investigational medicinal product code	HDM201
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

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. Subjects were dosed at 20 mg.

Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection, Powder for solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Azacitidine was provided in 100 mg (formulation provided as approved by regulations) was provided as powder for suspension for injection, or powder for solution for subcutaneous injection or intravenous infusion.

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Venetoclax was provided in the form of 10 mg, 50 mg and 100 mg tablets. Subjects were dosed at 400 mg dose per day.

Arm title	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats

Arm 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.

Arm type	Experimental
Investigational medicinal product name	Siremadlin
Investigational medicinal product code	HDM201
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

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. Subjects were dosed at 20 mg.

Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection, Powder for solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Azacitidine was provided in 100 mg (formulation provided as approved by regulations) was provided as powder for suspension for injection, or powder for solution for subcutaneous injection or intravenous infusion.

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Venetoclax was provided in the form of 10 mg, 50 mg and 100 mg tablets. Subjects were dosed at 400 mg dose per day.

Number of subjects in period 1	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats
Started	6	8
Did not enter post-treatment follow-up	4	6
Entered post-treatment f/u, discont.	2	1
Safety Set	6	8
Full Analysis Set (FAS)	6	7
Excluded from FAS due to TP53	0	1
Completed	0	0
Not completed	6	8
Adverse event, serious fatal	3	7
Subject Decision	1	-

Excluded from FAS due to TP53 & died	-	1
Study Terminated by Sponsor	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1: Adult participants with unfit AML
Reporting 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.	
Reporting group title	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats
Reporting 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.	

Reporting group values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats	Total
Number of subjects	6	8	14
Age Categorical Units: Participants			
< 65 years	1	0	1
>= 65 years	5	8	13
Sex: Female, Male Units: participants			
Female	4	3	7
Male	2	5	7
Race/Ethnicity, Customized Units: Subjects			
White	6	4	10
Asian	0	4	4

End points

End points reporting groups

Reporting group title	Arm 1: Adult participants with unfit AML

Reporting 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.

Reporting group title	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats

Reporting 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.

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

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

End point 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.

End point type	Primary

End point timeframe:

From Cycle 1 Day 1 to Cycle 1 Day 28; Cycle = 28 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical analysis was done.

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	7		
Units: Percentage of Participants				
number (not applicable)	0.0	14.29		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants achieving a complete remission (CR) rate as per

investigator assessment (Arm 1 only: Safety run-in part)

End point title	Percentage of participants achieving a complete remission (CR) rate as per investigator assessment (Arm 1 only: Safety run-in part)[2][3]

End point 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).

End point type	Primary

End point timeframe:

Day 14, Day 28, Day 56 and then every 84 days; end of treatment; estimated median time on follow-up was 57 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical analysis was done.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No Statistical analysis was done.

End point values	Arm 1: Adult participants with unfit AML			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Percentage of participants				
number (not applicable)	16.67			

Statistical analyses

No statistical analyses for this end point

Secondary: 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)

End point title	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)

End point 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.

End point type	Secondary

End point timeframe:

Day 14, Day 28, Day 56 and then every 84 days; end of treatment

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

[4] - No subjects were analyzed for this endpoint as the study was terminated.

[5] - No subjects were analyzed for this endpoint as the study was terminated.

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of participants achieving complete remission (CR) as per Investigator assessment - Arm 2 only (Part 1: Safety run-in part)[6]

End point 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).

End point type	Secondary

End point timeframe:

Day 14, Day 28, Day 56 and then every 84 days; end of treatment; estimated median time on follow-up was 66 days

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No Statistical analysis was done.

End point values	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Percentage of participants				
number (not applicable)	0.0			

Statistical analyses

No statistical analyses for this end point

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

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

End point 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).

End point type	Secondary

End point timeframe:

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

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: Percentage of participants				
number (not applicable)	16.67	14.29		

Statistical analyses

No statistical analyses for this end point

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

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

End point 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).

End point type	Secondary

End point timeframe:

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

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: Percentage of participants				
number (not applicable)	16.67	42.86		

Statistical analyses

No statistical analyses for this end point

Secondary: 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)

End point title	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)

End point 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.

End point type	Secondary

End point timeframe:

Day 14, Day 28, Day 56 and then every 84 days; end of treatment

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

[7] - No subjects were analyzed for this endpoint as the study was terminated.

[8] - No subjects were analyzed for this endpoint as the study was terminated.

Statistical analyses

No statistical analyses for this end point

Secondary: 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)

End point title	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)

End point 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.

End point type	Secondary

End point timeframe:

Day 14, Day 28, Day 56 and then every 84 days; end of treatment

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

[9] - No subjects were analyzed for this endpoint as the study was terminated.

[10] - No subjects were analyzed for this endpoint as the study was terminated.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

OS is the time from start of treatment to death due to any cause.

End point type	Secondary

End point timeframe:

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)

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

[11] - No subjects were analyzed for this endpoint as the study was terminated.

[12] - No subjects were analyzed for this endpoint as the study was terminated.

Statistical analyses

No statistical analyses for this end point

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

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

End point 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).

End point type	Secondary

End point timeframe:

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

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	8		
Units: h*ng/mL				
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 (± 0)	1689 (± 0)		
AUC0-24h: Siremadlin C5D5 (n = 0, 1)	0 (± 0)	1466 (± 0)		
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 (± 0)	1755 (± 0)		
AUClast: Siremadlin C5D5 (n = 0, 1)	0 (± 0)	1495 (± 0)		
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 (± 0)	6503 (± 0)		
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 (± 0)	6557 (± 0)		
AUClast: Venetoclax C5D5 (n = 0, 1)	0 (± 0)	50109 (± 0)		

Statistical analyses

No statistical analyses for this end point

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

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

End point 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.

End point type	Secondary

End point timeframe:

30 days & 60 days from start of study treatment

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: Percentage of participants				
number (not applicable)				
Death in first 30 days from treatment start	0.0	14.29		
Death in first 60 days from treatment start	33.33	28.57		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

AUC0-3h and 6h: The area under the concentration vs. time Curve (AUC) from time zero to specified time point.

End point type	Secondary

End point timeframe:

Cycle 1 and 5 at Day 1 pre-dose, 0.5 h, 1 h, 2 h, 3 h, 6 h; Cycle = 28 Days

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
AUC0-3h: C1D1(n = 3, 8)	1162 (± 79.0)	621 (± 155.0)		

AUC0-3h: C5D1 (n = 0, 1)	0 (± 0)	694 (± 0)		
AUC0-6h: C1D1 (n = 3, 6)	1302 (± 69.2)	1042 (± 39.1)		
AUC0-6h: C5D1 (n = 0, 1),	0 (± 0)	951 (± 0)		
AUClast: C1D1 (n = 4, 8)	979 (± 83.2)	587 (± 179.5)		
AUClast: C5D1 (n = 0, 1)	0 (± 0)	951 (± 0)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Cmax is the maximum (peak) observed plasma, blood, serum or other body fluid drug concentration following drug administration (mass x volume -1)

End point type	Secondary

End point timeframe:

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

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	8		
Units: ng/mL				
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 (± 0)	100 (± 0)		
Siremadlin: C5D5 (n = 0, 1)	0 (± 0)	80 (± 0)		
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 (± 0)	358 (± 0)		
Venetoclax: C5D5 (n = 0, 1)	0 (± 0)	2840 (± 0)		

Statistical analyses

No statistical analyses for this end point

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

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

End point 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.

End point type	Secondary

End point timeframe:

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

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	8		
Units: hours				
median (full range (min-max))				
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)	0 (0 to 0)	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)	0 (0 to 0)	10.0 (10.0 to 10.0)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Cmax is the maximum (peak) observed plasma, blood, serum or other body fluid drug concentration following drug administration (mass x volume -1)

End point type	Secondary

End point timeframe:

Cycle 1 and 5 at Day 1 pre-dose, 0.5 h, 1 h, 2 h, 3 h, 6 h; Cycle = 28 Days

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1 (n = 4, 8)	787 (± 70.2)	543 (± 114.9)		
C5D1 (n = 0, 1)	0 (± 0)	541 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: 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)

End point title	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)

End point 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.

End point type	Secondary

End point timeframe:

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

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: Percentage of participants				
number (not applicable)	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

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

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

End point 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.

End point type	Secondary

End point timeframe:

Cycle 1 and 5 at Day 1 pre-dose, 0.5 h, 1 h, 2 h, 3 h, 6 h; Cycle = 28 Days

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: hours				
median (full range (min-max))				
C1D1	0.62 (0.4 to 1.0)	0.5 (0.3 to 2.0)		
C5D1 (n = 0, 1)	0 (0 to 0)	0.5 (0.5 to 0.5)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

End point title	All Collected Deaths

End point 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.

End point type	Post-hoc

End point timeframe:

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

End point values	Arm 1: Adult participants with unfit AML	Arm2:Adult parts wth newly diag unfit AML/high-risk clin feats		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	8		
Units: Participants				
Total Deaths	3	8		
On-treatment deaths	1	4		
Post-treatment deaths	2	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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.

Adverse event reporting 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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Arm 2@HDM201+AZA+VEN

Reporting group description:

Arm 2@HDM201+AZA+VEN

Reporting group title	Arm 1@HDM201+AZA+VEN

Reporting group description:

Arm 1@HDM201+AZA+VEN

Serious adverse events	Arm 2@HDM201+AZA+VEN	Arm 1@HDM201+AZA+VEN	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	6 / 6 (100.00%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	3 / 8 (37.50%)	2 / 6 (33.33%)	
occurrences causally related to treatment / all	3 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 8 (25.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 8 (25.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 8 (25.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm 2@HDM201+AZA+VEN	Arm 1@HDM201+AZA+VEN	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	5 / 6 (83.33%)	
Vascular disorders			
Subclavian vein occlusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Thrombophlebitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 8 (25.00%)	2 / 6 (33.33%)	
occurrences (all)	2	2	
Chills			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Fat necrosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Injection site pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Mucosal inflammation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pyrexia			

subjects affected / exposed	2 / 8 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Confusional state			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Delirium			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Antithrombin III decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Enterococcus test positive			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
International normalised ratio increased			

subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Oxygen saturation decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	
occurrences (all)	1	6	
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	2 / 8 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
White blood cell count decreased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Injury, poisoning and procedural complications			
Jaw fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Lip injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Skin laceration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	3	
Palpitations			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Bundle branch block left			

subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 8 (37.50%)	2 / 6 (33.33%)	
occurrences (all)	5	2	
Cytopenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pancytopenia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Neutropenia			
subjects affected / exposed	5 / 8 (62.50%)	2 / 6 (33.33%)	
occurrences (all)	19	6	
Leukopenia			
subjects affected / exposed	2 / 8 (25.00%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Febrile neutropenia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Thrombocytopenia			
subjects affected / exposed	6 / 8 (75.00%)	1 / 6 (16.67%)	
occurrences (all)	15	1	
Eye disorders			

Retinal haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Paraesthesia oral			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	3 / 8 (37.50%)	1 / 6 (16.67%)	
occurrences (all)	5	1	
Oesophageal spasm			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	3 / 8 (37.50%)	3 / 6 (50.00%)	
occurrences (all)	3	3	
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	2 / 8 (25.00%)	3 / 6 (50.00%)	
occurrences (all)	3	3	
Aphthous ulcer			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Anal haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Anal fistula			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Constipation			

subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Ecchymosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Purpura			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

Pneumonia fungal			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Sinusitis fungal			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 8 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Hyperphosphataemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	4 / 8 (50.00%)	1 / 6 (16.67%)	
occurrences (all)	8	1	
Hypomagnesaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypophosphataemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2021	In response to the request from Health Authorities, the inclusion criteria were revised. The amendment included: Clarification on inclusion criterion 4 regarding ineligibility of participants for standard induction chemotherapy, to be determined for both arms' participant population prior to initiation of standard of care venetoclax plus azacitidine treatment; particularly for Arm 1 participants, who received first line venetoclax plus azacitidine treatment prior to study entry. Inclusion criterion 9 was amended to specify that participants with an estimated glomerular filtration rate (eGFR)≥ 60 mL/min/1.73 m2, were eligible for the study. Amendment also specified that siremadlin would be discontinued in case of Grade 4 hyperbilirubinemia in the guidance for dose modification. Clarification regarding Tumor Lysis Syndrome (TLS) prophylactic treatments options were added. Additional, ECHO (or MUGA scan) was added at screening visit (and during treatment, if clinically indicated) for the evaluation of cardiac function.
03 August 2022	Protocol was amended to update the dose modifications guidelines of the study treatment based on participant's efficacy response and associated hematological toxicities. The amendment adopted 2022 European Leukemia Net (ELN) 2022 genetic risk classification and AML response criteria (Döhner et al 2022). Dose modification guidelines for hepatic adverse reaction were updated, and the follow-up for participants with QTcF prolongations was clarified.
28 April 2023	The protocol was amended on February 24, 2023, to implement Urgent Safety Measures addressing severe neutropenia and thrombocytopenia. Changes included dose modification and early treatment interruption starting from Cycle 1, along with a mandatory bone marrow assessment at C1D14 for all participants. Guidance was provided on prophylactic anti-infective therapy and G-CSF use. Venetoclax dose modification was updated, considering a minimum exposure criterion at Cycle 1 for the Dose Determining Set, with the planned dose reduced from 75% to 50%. Clarifications were made regarding the prior use of Hypomethylating agents (HMA) for treating primary MDS, excluding participants with an antecedent diagnosis of myelofibrosis during the safety-run and enrolling them only in the expansion part of the study. Participants previously treated with FLT-3 inhibitors and checkpoint inhibitors were excluded. Flexibility for PK sample collection was adjusted to +/- 2 hours for the 12-hour and 24-hour post-dose timepoints in the safety run-in phase. Emphasis was placed on caution or action against the use of strong or moderate CYP3A inhibitors or P-gp inhibitors. The azacitidine SmPC was updated to extend the mandatory contraception period for female participants from 3 to 6 months. Clear guidance was provided on overdose management and dose modification for isolated Grade 2 bilirubin increases.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported