



Clinical trial results:

Phase I/II, international, multicentre, open-label, non-randomised, non-comparative study evaluating the safety, tolerability and clinical activity of intravenously administered S64315, a selective Mcl-1 inhibitor, in combination with azacitidine in patients with acute myeloid leukaemia (AML)

Summary

EudraCT number	2019-004896-38
Trial protocol	FR
Global end of trial date	25 August 2023

Results information

Result version number	v1 (current)
This version publication date	28 April 2024
First version publication date	28 April 2024

Trial information

Trial identification

Sponsor protocol code	CL1-64315-004
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04629443
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 136541

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier (I.R.I.S.)
Sponsor organisation address	50 rue Carnot, Suresnes Cedex, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.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	25 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 August 2023
Global end of trial reached?	Yes
Global end of trial date	25 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety profile (including Dose-Limiting Toxicities (DLTs) and Maximum Tolerated Dose (MTD)) and tolerability of S64315 in combination with azacitidine in patients with Acute Myeloid Leukaemia (AML).

This study was originally designed as 2 phases: Phase I for dose escalation and Phase II for dose expansion. The dose escalation Phase I part was further planned to have 2 arms: (Arm A and Arm B). However, the Phase I (Arm B) and Phase II (dose expansion) were not conducted due to recruitment discontinuation. Phase I of the study was only conducted.

Protection of trial subjects:

The study was conducted in compliance with the protocol, GCP, ethical principles of the Declaration of Helsinki and the applicable regulatory requirements. All the patients were to give freely their written informed consent before the start of the screening process of the study.

Background therapy: -

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	17
EEA total number of subjects	13

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)	7
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Investigators were oncologists.

Pre-assignment

Screening details:

Patients at age 18+ years with cytologically confirmed and documented de novo, secondary or therapy-related AML:

-With relapsed or refractory disease and without established alternative therapy

-Secondary to myelodysplastic syndrome treated and without established alternative therapy

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study. No study medication blinding was required.

Arms

Are arms mutually exclusive?	Yes
Arm title	50 mg of S64315 + 75 mg/m ² of azacitidine

Arm description:

Patients received 50 mg S64315 in combination with 75 mg/m² of azacitidine following the study treatment scheme.

Arm type	Experimental
Investigational medicinal product name	S64315, 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

S64315 was administered via intravenous (IV) infusion over at least 2 hours, once a week. During the Lead-in Dose period S64315 was administered in quantity of 25 mg at D-13 and 50 mg at D-6. In treatment period 50 mg S64315 were administered weekly of each 28-day cycles (Cx) i.e. on CxD2, CxD9, CxD16 and CxD23. On days of concomitant administration of S64315 and azacitidine (CxD2), azacitidine was administered 2 hours prior to S64315.

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

Dosage and administration details:

Azacitidine was administered via subcutaneous (SC) injection, once a day over 7 consecutive days. 75 mg/m² of azacitidine administered daily for 7 days from CxD1 to CxD7 followed by a rest period of 21 days. On days of concomitant administration of S64315 and azacitidine (CxD2), azacitidine was administered 2 hours prior to S64315.

Arm title	100 mg of S64315 + 75 mg/m ² of azacitidine
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Arm description:

Patients received 100 mg S64315 in combination with 75 mg/m² of azacitidine following the study treatment scheme.

Arm type	Experimental
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Investigational medicinal product name	S64315, 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

S64315 was administered via intravenous (IV) infusion over at least 2 hours, once a week. During the Lead-in Dose period S64315 was administered in quantity of 25 mg at D-13 and 50 mg at D-6. In treatment period 100 mg S64315 were administered weekly of each 28-day cycles (Cx) i.e. on CxD2, CxD9, CxD16 and CxD23. On days of concomitant administration of S64315 and azacitidine (CxD2), azacitidine was administered 2 hours prior to S64315.

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

Dosage and administration details:

Azacitidine was administered via subcutaneous (SC) injection, once a day over 7 consecutive days. 75 mg/m² of azacitidine administered daily for 7 days from CxD1 to CxD7 followed by a rest period of 21 days. On days of concomitant administration of S64315 and azacitidine (CxD2), azacitidine was administered 2 hours prior to S64315.

Arm title	190 mg of S64315 + 75 mg/m ² of azacitidine
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Arm description:

Patients received 190 mg S64315 in combination with 75 mg/m² of azacitidine following the study treatment scheme.

Arm type	Experimental
Investigational medicinal product name	S64315, 190 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

S64315 was administered via intravenous (IV) infusion over at least 2 hours, once a week. During the Lead-in Dose period S64315 was administered in quantity of 25 mg at D-13 and 50 mg at D-6. In treatment period 190 mg S64315 were administered weekly of each 28-day cycles (Cx) i.e. on CxD2, CxD9, CxD16 and CxD23. On days of concomitant administration of S64315 and azacitidine (CxD2), azacitidine was administered 2 hours prior to S64315.

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

Dosage and administration details:

Azacitidine was administered via subcutaneous (SC) injection, once a day over 7 consecutive days. 75 mg/m² of azacitidine administered daily for 7 days from CxD1 to CxD7 followed by a rest period of 21 days. On days of concomitant administration of S64315 and azacitidine (CxD2), azacitidine was administered 2 hours prior to S64315.

Number of subjects in period 1	50 mg of S64315 + 75 mg/m ² of azacitidine	100 mg of S64315 + 75 mg/m ² of azacitidine	190 mg of S64315 + 75 mg/m ² of azacitidine
Started	5	7	5
Completed	0	0	0
Not completed	5	7	5
Physician decision	1	3	-
Adverse event, non-fatal	2	1	2
Progressive disease	2	3	3

Baseline characteristics

Reporting groups

Reporting group title	50 mg of S64315 + 75 mg/m ² of azacitidine
Reporting group description: Patients received 50 mg S64315 in combination with 75 mg/m ² of azacitidine following the study treatment scheme.	
Reporting group title	100 mg of S64315 + 75 mg/m ² of azacitidine
Reporting group description: Patients received 100 mg S64315 in combination with 75 mg/m ² of azacitidine following the study treatment scheme.	
Reporting group title	190 mg of S64315 + 75 mg/m ² of azacitidine
Reporting group description: Patients received 190 mg S64315 in combination with 75 mg/m ² of azacitidine following the study treatment scheme.	

Reporting group values	50 mg of S64315 + 75 mg/m ² of azacitidine	100 mg of S64315 + 75 mg/m ² of azacitidine	190 mg of S64315 + 75 mg/m ² of azacitidine
Number of subjects	5	7	5
Age categorical Units: Subjects			
Adults (18-64 years)	1	4	2
From 65-84 years	4	3	3
Age continuous Units: years			
arithmetic mean	71.6	60.1	64.8
standard deviation	± 8.3	± 14.1	± 12.9
Gender categorical Units: Subjects			
Female	1	3	3
Male	4	4	2

Reporting group values	Total		
Number of subjects	17		
Age categorical Units: Subjects			
Adults (18-64 years)	7		
From 65-84 years	10		
Age continuous Units: years			
arithmetic mean	-		
standard deviation	-		
Gender categorical Units: Subjects			
Female	7		
Male	10		

End points

End points reporting groups

Reporting group title	50 mg of S64315 + 75 mg/m ² of azacitidine
Reporting group description: Patients received 50 mg S64315 in combination with 75 mg/m ² of azacitidine following the study treatment scheme.	
Reporting group title	100 mg of S64315 + 75 mg/m ² of azacitidine
Reporting group description: Patients received 100 mg S64315 in combination with 75 mg/m ² of azacitidine following the study treatment scheme.	
Reporting group title	190 mg of S64315 + 75 mg/m ² of azacitidine
Reporting group description: Patients received 190 mg S64315 in combination with 75 mg/m ² of azacitidine following the study treatment scheme.	
Subject analysis set title	Safety Set
Subject analysis set type	Full analysis
Subject analysis set description: Safety Set (SS): All patients who signed the ICF and who received at least one dose of IMP (S64315 or azacitidine) during the dose escalation Phase I part of the study.	
Subject analysis set title	DLT-Evaluable Set (DLTES)
Subject analysis set type	Full analysis
Subject analysis set description: All patients from the SS who were evaluable for DLT according to the DLT assessment at the end of Cycle 1.	

Primary: Dose-limiting toxicity (DLT)

End point title	Dose-limiting toxicity (DLT) ^[1]
End point description: In the DLTES (N = 13), 2 patients experienced at least one DLT during the dose escalation: - 1 patient in the S64315 100 mg + 75 mg/m ² azacitidine dose level group. - 1 patient in the S64315 190 mg + 75 mg/m ² azacitidine dose level group.	
End point type	Primary
End point timeframe: Dose-limiting toxicity that occurred during LID or Cycle 1.	
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: Only descriptive statistical analyses were provided. The Maximum Tolerated Dose could not be determined.	

End point values	DLT-Evaluable Set (DLTES)			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Presence of DLTs				
Cardiac disorders	1			
Hepatic abnormalities	1			

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Since the administration of the first dose of the IMPs up to 30 calendar days after the participant's last IMP administration.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	50 mg of S64315 + 75 mg/m ² of azacitidine
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Reporting group description:

Patients randomized to received 50 mg S64315 in combination with 75 mg/m² of azacitidine following the study treatment scheme.

Reporting group title	100 mg of S64315 + 75 mg/m ² of azacitidine
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Reporting group description:

Patients randomized to received 100 mg S64315 in combination with 75 mg/m² of azacitidine following the study treatment scheme.

Reporting group title	190 mg of S64315 + 75 mg/m ² of azacitidine
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Reporting group description:

Patients randomized to received 190 mg S64315 in combination with 75 mg/m² of azacitidine following the study treatment scheme.

Serious adverse events	50 mg of S64315 + 75 mg/m ² of azacitidine	100 mg of S64315 + 75 mg/m ² of azacitidine	190 mg of S64315 + 75 mg/m ² of azacitidine
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	7 / 7 (100.00%)	4 / 5 (80.00%)
number of deaths (all causes)	2	1	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			

subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin I increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Skin injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral atrophy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 5 (80.00%)	2 / 7 (28.57%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anorectal cellulitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal sepsis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis aspergillus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	50 mg of S64315 + 75 mg/m ² of azacitidine	100 mg of S64315 + 75 mg/m ² of azacitidine	190 mg of S64315 + 75 mg/m ² of azacitidine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	6 / 7 (85.71%)	5 / 5 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 5 (40.00%)	1 / 7 (14.29%)	1 / 5 (20.00%)
occurrences (all)	3	1	1
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Administration site erythema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Impaired healing			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Injection site haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injection site rash			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 5 (20.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Pulmonary hypertension			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Investigations			

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	4 / 5 (80.00%) 6	2 / 7 (28.57%) 4	3 / 5 (60.00%) 3
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	2 / 7 (28.57%) 4	2 / 5 (40.00%) 3
Troponin T increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	2 / 7 (28.57%) 4	0 / 5 (0.00%) 0
Brain natriuretic peptide increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	1 / 5 (20.00%) 2
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0
Blood creatine phosphokinase MB increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Blood phosphorus decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1
Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 5 (20.00%) 3
Injury, poisoning and procedural complications			

Febrile nonhaemolytic transfusion reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Subdural haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Traumatic haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Neutropenia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	11	4	0
Thrombocytopenia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	6	1	0
Hyperleukocytosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Leukocytosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Ear and labyrinth disorders			

Deafness bilateral subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1
Vertigo subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1
Eye haemorrhage subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	4 / 5 (80.00%) 5	2 / 7 (28.57%) 2	0 / 5 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 7 (14.29%) 1	2 / 5 (40.00%) 2
Abdominal pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 3	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0
Anal fissure			

subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Aphthous ulcer			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gingival bleeding			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tongue ulceration			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Polyuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Proteinuria			

subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Renal impairment			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Urinary incontinence			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Device related sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Folliculitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Herpes simplex reactivation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			

Hypokalaemia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 7 (14.29%)	1 / 5 (20.00%)
occurrences (all)	2	2	3
Hypophosphataemia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 7 (0.00%)	2 / 5 (40.00%)
occurrences (all)	2	0	2
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Hypomagnesaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	6	0
Hyperuricaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Polydipsia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2021	<p>Amendment No. 1 was applicable in all countries. It mainly concerned:</p> <ul style="list-style-type: none">- Removal of non-screening criterion #6 (patients previously treated with HMA)- Modification of DLT definition for isolated AST or ALT elevation- Modification of treatment dose adaptations and readministration criteria based on AST or ALT values- Additional timepoints for monitoring of AST, ALT and total bilirubin- Update of criteria for study discontinuation during the LID period- Update on pharmacokinetic timepoints- Clarification of inclusion criteria 29- Update of exclusion criteria 43- Additional recommendations for management of IRR- Update of the reporting of fatal events during inclusion period- Modification of the deadlines for obtaining certain examinations for inclusion (Chest X-Ray and hepatitis markers)- Clarification in case of TLS Grade 3 or 4 in the protocol Table (8.12) 1- Clarification on cardiac marker samples- Update of the protocol Table (4.4.1) 1 in accordance with the investigational medicinal product dossier-Quality- Modification implemented in Not statistically Significant Amendment n°1- Typo corrections
25 November 2021	<p>Amendment No. 2 was applicable in all countries. It mainly concerned:</p> <ul style="list-style-type: none">- Updates following FDA's recommendations:<ul style="list-style-type: none">• Addition of safety stopping rules and dose modification rules in expansion part• Addition of study safety stopping rules for any death suspected to be related to S64315 occurring within 30 days of study treatment administration• Monitoring of DLTs implemented at all cycles of treatment in escalation and expansion parts• Update of DLT definition for haematologic toxicity and troponin increase• Update of eligibility criteria 16 and 43• Update of management of S64315 dose modifications for QTc interval, creatine phosphokinase elevation and troponin elevation• Update of dose modifications for non-hematologic toxicities• Sub-Arm A3 enrolling patients with newly diagnosed AML removed from the Phase II expansion part• Phase II expansion part primary objective updated to CR rate• Clarifications added on study design for the expansion cohorts• Addition of treatment failure definition- Addition of recommendation in case of coronavirus disease 2019 (COVID-19) infection- Addition of recommendation in case of C1D9 infusion missed- Implementation of non-substantial amendment #2

12 April 2022	<p>Amendment No. 3 was applicable in all countries. It mainly concerned:</p> <ul style="list-style-type: none"> - To allow the possibility to include more than 6 DLT-evaluable patients in a cohort - To remove the collection of blood samples for PK that are considered unnecessary - Update of blood sampling timepoints for PK - Update of blood sampling timepoints for peripheral blood mononuclear cells assessment - Change in instructions that one of the 2 IMPs is permanently discontinued or discontinued for more than 28 days - Update for re-starting of study treatment after COVID-19 infection - Clarification of wording related to treatment discontinuation during LID period (LID2 or C1D2) - Clarification about the investigations to be performed in the case of the need for an additional LID period - Clarification of the definition of DLT - Clarification about any new concomitant medication administration - Clarification in the wording of the one-week safety window between C1D2 of the first patient and C1D2 of subsequent patients in the same cohort - Clarification added in the situation where MTD is not be reached in some situations - Clarification for a secondary objective during expansion Phase II: CRi is defined according to ELN recommendations - Update of statistical analysis sets for the expansion Phase II part - Update for attesting authenticity of the data collected in the eCRF
14 October 2022	<p>Amendment No. 4 was applicable in all countries. It mainly concerned:</p> <ul style="list-style-type: none"> - Update of inclusion criteria #13 due to EU SmPC of azacitidine update (April 2022)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported