Clinical trial results:
A Phase II Study with a Safety Run-in Phase Evaluating Vosaroxin With Azacitidine in Older Patients with Newly Diagnosed Acute Myeloid Leukemia and Intermediate/Adverse Genetic Risk or Myelodysplastic Syndrome with Excess Blasts-2 (MDS-EB-2) - AMLSG 24-15

Summary

EudraCT number	2015-004066-28
Trial protocol	DE
Global end of trial date	31 October 2019

Results information

Result version number	v1 (current)
This version publication date	13 November 2020
First version publication date	13 November 2020
Summary attachment (see zip file)	AMLSG 24-15 Final report (AMLSG 24-15_Ergebnisbericht_Oct_2020_FINAL.pdf)

Trial information

Trial identification

Sponsor protocol code	AMLSG2415

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03338348
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Ulm
Sponsor organisation address	Albert-Einstein-Allee 23, Ulm, Germany, 89081
Public contact	Verena Gaidzik, Universiy Hospital Ulm, +49 73150045707, daniela.weber@uniklinik-ulm.de
Scientific contact	Verena Gaidzik, University Hospital Ulm, 3150045980 73150045707, daniela.weber@uniklinik-ulm.de

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 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 October 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary Efficacy Objective
- The primary efficacy objective is to evaluate the effect of vosaroxin in combination with azacitidine on the rate of complete remission (CR) and CR with incomplete blood count recovery (CRi) in older (≥60 years) patients with newly diagnosed AML or MDS-EB-2, who are unlikely to benefit from standard intensive chemotherapy

Key Secondary Efficacy Objective
- To conduct a pre-defined subgroup analysis in older (≥60 years) patients with complex karyotype to evaluate the effect of vosaroxin in combination with azacitidine on CR and CRi

Secondary Efficacy Objectives
- To evaluate the rate of CR and rate of combined CR/CRi and CR with negativity for minimal residual disease (CRMRD-)
- To analyze duration of response (DOR)
- To evaluate event-free survival (EFS)
- To evaluate overall survival (OS)

Safety and QoL Objectives
- Incidence and intensity of adverse events (AEs) with vosaroxin in combination with azacitidine as assess

Protection of trial subjects:

In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, chest X-ray, echo scan, physical examination findings, monitoring of concomitant therapy. For each safety parameter, all findings (whether normal or abnormal) were recorded in the eCRF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 May 2018
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	Germany: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	0
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First Patient in: 14.05.2018
Last Patient in: 22.05.2019
Nine patients were recruited within the safety run-in phase at 11 participating sites in Germany. On Oct 31th 2019 the study was early terminated, since the manufacturer of Vosaroxin, SUNESIS Pharmaceuticals, Inc., had discontinued the development programme of the IMP Vosaroxin.

Pre-assignment

Screening details:

Screening details:
Molecular genetic analysis (central AMLSG reference lab) of blood and bone marrow was performed at baseline within 48 hours to make an enrollment possible.

Period 1

Period 1 title	Safety run-in phase (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Study treatment

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Vosaroxin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Vosaroxin is administered up to 8 cycles on day 1 to 7.
Dose levels safety run-in Phase:
Dose level 0: 70mg/m²
Dose level -1: 50mg/m²
Dose level -2: 40mg/m²

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

Dosage and administration details:

Patients will receive up to 8 cycles of azacitidine at 75 mg/m²/d on days 1-7 (in combination with vosaroxin). Patients who have
completed 8 cycles of azacitidine are scheduled to maintenance with
single agent azacitidine at 75 mg/m²/d on days 1-7 until relapse or progression.

Number of subjects in period 1	Study treatment
Started	9
Completed	0
Not completed	9
Adverse event, serious fatal	1
Physician decision	1
Allogeneic stem cell transplantation	1
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Other reason	1
Lack of efficacy	3

Baseline characteristics

Reporting groups	
Reporting group title	Safety run-in phase

Reporting group description: -

Reporting group values	Safety run-in phase	Total	
Number of subjects	9	9	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	71.4		
full range (min-max)	65.8 to 81.8	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	8	8	
Ethnicity Units: Subjects			
Caucasian	9	9	
Asian	0	0	
North African/Arabian/Turk	0	0	
Other African	0	0	
Other	0	0	
WHO ECOG performance status Units: Subjects			
ECOG 0	8	8	
ECOG 1	0	0	
ECOG 2	1	1	
ECOG 3	0	0	
ECOG 4	0	0	
Initial diagnosis Units: Subjects			
AML	8	8	
MDS RAEB-2	1	1	
Type of AML Units: Subjects			

De novo AML	2	2	
Secondary AML after MDS/MPS	6	6	
Treatment-related AML	0	0	
Missing	1	1	
ELN classification AML Units: Subjects			
Favorable	0	0	
Intermediate	1	1	
Adverse	7	7	
Missing	1	1	
FLT3-ITD Units: Subjects			
Negative	8	8	
FLT3-ITD low	1	1	
FLT3-ITD high	0	0	
FLT3-TKD Units: Subjects			
Negative	9	9	
Positive	0	0	
NPM1 Units: Subjects			
Wildtype	9	9	
Mutation	0	0	
CEBPA Units: Subjects			
Wildtype	9	9	
Mono-allelic mutation	0	0	
Bi-allelic mutation	0	0	
ASXL1 Units: Subjects			
Wildtype	1	1	
Mutation	3	3	
Missing	5	5	
RUNX1 Units: Subjects			
Wildtype	1	1	
Mutation	3	3	
Missing	5	5	
TP53 Units: Subjects			
Wildtype	4	4	
Mutation	0	0	
Missing	5	5	
CIRS score Units: Points			
median	2		
full range (min-max)	1 to 11	-	
LDH Units: U/l			
median	219		
full range (min-max)	119 to 620	-	

Hemoglobin Units: g/dl median full range (min-max)	 9.2 7.5 to 13.2	 -	
Platelets Units: G/l median full range (min-max)	 77 12 to 437	 -	
White blood count Units: G/l median full range (min-max)	 2.5 0.5 to 52.8	 -	
Bone marrow blast Units: Percent median full range (min-max)	 25 9 to 50	 -	
Peripheral blood blast Units: Percent median full range (min-max)	 0 0 to 10	 -	

Subject analysis sets	
Subject analysis set title	ITT analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT Analysis set contains all patients enrolled into the trial	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Analysis set contains all patients which received at least one dose of Azacitidine or Vosaroxin.	

Reporting group values	ITT analysis set	Safety analysis set	
Number of subjects	9	9	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median full range (min-max)	 71.4 65.8 to 81.8	 71.4 65.8 to 81.8	

Gender categorical Units: Subjects			
Female	1	1	
Male	8	8	
Ethnicity Units: Subjects			
Caucasian	9	9	
Asian	0	0	
North African/Arabian/Turk	0	0	
Other African	0	0	
Other	0	0	
WHO ECOG performance status Units: Subjects			
ECOG 0	8	8	
ECOG 1	0	0	
ECOG 2	1	1	
ECOG 3	0	0	
ECOG 4	0	0	
Initial diagnosis Units: Subjects			
AML	8	8	
MDS RAEB-2	1	1	
Type of AML Units: Subjects			
De novo AML	2	2	
Secondary AML after MDS/MPS	6	6	
Treatment-related AML	0	0	
Missing	1	1	
ELN classification AML Units: Subjects			
Favorable	0	0	
Intermediate	1	1	
Adverse	7	7	
Missing	1	1	
FLT3-ITD Units: Subjects			
Negative	8	8	
FLT3-ITD low	1	1	
FLT3-ITD high	0	0	
FLT3-TKD Units: Subjects			
Negative	9	9	
Positive	0	0	
NPM1 Units: Subjects			
Wildtype	9	9	
Mutation	0	0	
CEBPA Units: Subjects			
Wildtype	9	9	
Mono-allelic mutation	0	0	

Bi-allelic mutation	0	0	
ASXL1 Units: Subjects			
Wildtype	1	1	
Mutation	3	3	
Missing	5	5	
RUNX1 Units: Subjects			
Wildtype	1	1	
Mutation	3	3	
Missing	5	5	
TP53 Units: Subjects			
Wildtype	4	4	
Mutation	0	0	
Missing	5	5	
CIRS score Units: Points			
median	2	2	
full range (min-max)	1 to 11	1 to 11	
LDH Units: U/l			
median	219	219	
full range (min-max)	119 to 620	119 to 620	
Hemoglobin Units: g/dl			
median	9.2	9.2	
full range (min-max)	7.5 to 13.2	7.5 to 13.2	
Platelets Units: G/l			
median	77	77	
full range (min-max)	12 to 437	12 to 437	
White blood count Units: G/l			
median	2.5	2.5	
full range (min-max)	0.5 to 52.8	0.5 to 52.8	
Bone marrow blast Units: Percent			
median	25	25	
full range (min-max)	9 to 50	9 to 50	
Peripheral blood blast Units: Percent			
median	0	0	
full range (min-max)	0 to 10	0 to 10	

End points

End points reporting groups

Reporting group title	Study treatment
Reporting group description: -	
Subject analysis set title	ITT analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT Analysis set contains all patients enrolled into the trial	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Analysis set contains all patients which received at least one dose of Azacitidine or Vosaroxin.	

Primary: Rate of complete remission / complete remission with incomplete hematological recovery

End point title	Rate of complete remission / complete remission with incomplete hematological recovery[1]
End point description:	
End point type	Primary
End point timeframe: during treatment phase (12 months)	

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: Primary and secondary efficacy variables were not analyzed due to premature termination of the trial.

End point values	Study treatment	ITT analysis set	Safety analysis set	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	9	9	
Units: Patients				
CR/CRi	4	4	4	
No response	5	5	5	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During treatment cycles and maintenance therapy (12 months)

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Overall treatment period

Reporting group description: -

Serious adverse events	Overall treatment period		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	1		
Investigations			
Other (Hepatic enzymes increased)			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Other (Bifascicular block)			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Mucositis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	1 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall treatment period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Vascular disorders			
Hematoma			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Hypertension			

subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	5		
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Superficial thrombophlebitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Edema limbs			
subjects affected / exposed	6 / 9 (66.67%)		
occurrences (all)	9		
Fatigue			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	9		
Fever			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	6		
Injection site reaction			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	13		
Non-cardiac chest pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Prostatic obstruction			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Dyspnea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Hiccups			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	8		
Restlessness			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Investigations			
Creatinine increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Electrocardiogram QT corrected interval prolonged			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Lymphocyte count decreased			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	3		
Other (LDH increase)			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	7 / 9 (77.78%)		
occurrences (all)	22		
Platelet count decreased			
subjects affected / exposed	9 / 9 (100.00%)		
occurrences (all)	27		
Weight gain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
White blood cell decreased			
subjects affected / exposed	8 / 9 (88.89%)		
occurrences (all)	27		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Other			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Ventricular arrhythmia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	5		
Syncope			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

Anemia subjects affected / exposed occurrences (all)	9 / 9 (100.00%) 32		
Other subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Febrile neutropenia subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 4		
Leukocytosis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 3		
Lymph node pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Thrombotic thrombocytopenic purpura subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Scleral disorder subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	7 / 9 (77.78%) 10		
Diarrhea subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 5		

Dry mouth subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Dyspepsia subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 3		
Mukositis oral subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 4		
Nausea subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 15		
Oral hemorrhage subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 3		
Periodontal disease subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Stomach pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Vomiting subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 4		
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Rash akneiform subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Rash maculo-papular subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 4		
Other			

subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Skin ulceration			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Renal and urinary disorders			
Other (fluid retention, edema)			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	3		
Urinary incontinence			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Chest wall pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infections and infestations			
Enterocolitis infectious			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Other			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Lip infection			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Mucosal infection subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Pharyngitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Sepsis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Sinusitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Skin infection subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2		
Tooth infection subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 6		
Hypoalbuminemia subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Hypocalcemia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2		
Hypokalemia subjects affected / exposed occurrences (all)	7 / 9 (77.78%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

On October 31st 2019 the study was early terminated, since the manufacturer of vosaroxin, SUNESIS Pharmaceuticals, Inc., had discontinued the development program of the IMP. Primary and secondary efficacy variables were not analyzed.

Notes: