Clinical trial results:
Comparison between 5 – azacytidine treatment and 5 – azacytidine followed by allogeneic stem cell transplantation in elderly patients with advanced MDS according to donor availability

Summary

EudraCT number	2010-018467-42
Trial protocol	DE
Global end of trial date	31 January 2019

Results information

Result version number	v1 (current)
This version publication date	29 September 2021
First version publication date	29 September 2021
Summary attachment (see zip file)	Clinical study report Synopsis (CTC09356_VidazaAlloStudy_ Clinical study report Synopsis 2021_03_31 Version 2.0_fully signed.pdf)

Trial information

Trial identification

Sponsor protocol code	VidazaAlloStudy

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Hamburg Eppendorf
Sponsor organisation address	Martinistrasse 52, Hamburg, Germany, 20246
Public contact	Principal Investigator, University Medical Center Hamburg Eppendorf, +49 40741055864, n.kroeger@uke.uni-hamburg.de
Scientific contact	Principal Investigator, University Medical Center Hamburg Eppendorf, +49 40741055864, n.kroeger@uke.uni-hamburg.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	13 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2019
Global end of trial reached?	Yes
Global end of trial date	31 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the overall survival at three years of patients who receive after 4 cycles of 5-azacytidine (Vidaza®) either allogeneic stem cell transplantation or continuous 5-azacytidine (Vidaza®) if no compatible donor is available.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, the general principles indicated in the Declaration of Helsinki, and all applicable regulatory requirements. Prior to study initiation the study protocol was reviewed and approved by an Independent Ethics Committee (IEC). The study, all study procedures and the risks and benefits were explained to the subjects by responsible investigators and written informed consent were collected prior to any study related examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 July 2011
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	Germany: 108
Worldwide total number of subjects	108
EEA total number of subjects	108

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)	65
From 65 to 84 years	43

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in Germany. 15 active study centers were involved.

Pre-assignment

Screening details:

- Screening periode: up to 28 days before first day of 5-Azacytidine administration
- Pre-assignement period: start with 4 cycles of 5-azacytidine

Pre-assignment period milestones

Number of subjects started	162[1]
Number of subjects completed	108

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, serious fatal: 12
Reason: Number of subjects	patient progressed: 26
Reason: Number of subjects	Adverse event, non-fatal: 7
Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	others: 7

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: There were 190 patients assessed for eligibility. 20 patients were screening failures + 8 patients were discontinued from study for other reasons. 162 patients started the pre-assignement period (Start with 4 cycles of 5-azacytidine).

Period 1

Period 1 title	Treatment Period (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 A: continued 5-Azacitidine

Arm description:

After 4 cycles of 5-aza all patients with response or stable disease were assigned to arm A (continued 5-azacyidine) until disease progression or unacceptable toxicity if no HLA compatible (10/10 alleles) donor had been found.

Arm type	Active comparator
Investigational medicinal product name	5-Azacyidine
Investigational medicinal product code	
Other name	Vidaza
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

5-azacytidine 75 mg/m² day 1-7 (qd 28)

Arm title	Arm B: Allogeneic stem cell transplantation

Arm description:

After 4 cycles of 5-aza all patients with response or stable disease were assigned to arm B if an HLA-compatible donor had been identified (10/10 alleles). Patients assigned to allogeneic stem cell

transplantation could receive up to 6 cycles of 5-aza if transplantation could not be performed immediately.

Arm type	Experimental
Investigational medicinal product name	Allogeneic hematopoietic stem cells (allo-HSC)
Investigational medicinal product code	
Other name	CD34+/ CD45+-cells
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

4-8 × 106 CD34+/ CD45+-cells per kg of body weight (allogen)

Number of subjects in period 1	Arm A: continued 5-Azacitidine	Arm B: Allogeneic stem cell transplantation
Started	27	81
Completed	27	81

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: continued 5-Azacitidine
Reporting group description:	
After 4 cycles of 5-aza all patients with response or stable disease were assigned to arm A (continued 5-azacyidine) until disease progression or unacceptable toxicity if no HLA compatible (10/10 alleles) donor had been found.	
Reporting group title	Arm B: Allogeneic stem cell transplantation
Reporting group description:	
After 4 cycles of 5-aza all patients with response or stable disease were assigned to arm B if an HLA-compatible donor had been identified (10/10 alleles). Patients assigned to allogeneic stem cell transplantation could receive up to 6 cycles of 5-aza if transplantation could not be performed immediately.	

Reporting group values	Arm A: continued 5-Azacitidine	Arm B: Allogeneic stem cell transplantation	Total
Number of subjects	27	81	108
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	13	52	65
From 65-84 years	14	29	43
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	17	25	42
Male	10	56	66

End points

End points reporting groups

Reporting group title	Arm A: continued 5-Azacitidine

Reporting group description:

After 4 cycles of 5-aza all patients with response or stable disease were assigned to arm A (continued 5-azacyidine) until disease progression or unacceptable toxicity if no HLA compatible (10/10 alleles) donor had been found.

Reporting group title	Arm B: Allogeneic stem cell transplantation

Reporting group description:

After 4 cycles of 5-aza all patients with response or stable disease were assigned to arm B if an HLA-compatible donor had been identified (10/10 alleles). Patients assigned to allogeneic stem cell transplantation could receive up to 6 cycles of 5-aza if transplantation could not be performed immediately.

Primary: Overall survival at three years between both treatment arms

End point title	Overall survival at three years between both treatment arms

End point description:

To compare the overall survival at three years of patients who receive after 4 cycles of 5-azacytidine (Vidaza®) (and achieve at least stable disease) either allogeneic stem cell transplantation or continuous 5-azacytidine (Vidaza®) if no compatible donor is available.

End point type	Primary

End point timeframe:

three years after start in both arms

End point values	Arm A: continued 5-Azacitidine	Arm B: Allogeneic stem cell transplantation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	81		
Units: percentage	32	50		

Statistical analyses

Statistical analysis title	Primary statistical analysis

Statistical analysis description:

The primary endpoint overall survival at three years between both treatment arms was analysed with a two-sided z-test based on the Kaplan-Meier rates by using Greenwood’s formula. All two-sided alphas were 5%. One hundred and twelve days were added to all rates to represent the initial 5-aza therapy.

Comparison groups	Arm A: continued 5-Azacitidine v Arm B: Allogeneic stem cell transplantation

Number of subjects included in analysis	108
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.5
Method	t-test, 2-sided

Secondary: Comparison of event free survival in both treatment arms

End point title	Comparison of event free survival in both treatment arms

End point description:

events being disease progression, relapse after complete remission or partial remission, death from any cause

End point type	Secondary

End point timeframe:

at three years

End point values	Arm A: continued 5-Azacitidine	Arm B: Allogeneic stem cell transplantation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	81		
Units: percentage	0	34		

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of treatment-related mortality in both treatment arms

End point title	Comparison of treatment-related mortality in both treatment arms

End point description:

End point type	Secondary

End point timeframe:

at 1 year

End point values	Arm A: continued 5-Azacitidine	Arm B: Allogeneic stem cell transplantation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	81		
Units: percentage	0	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of response rate in both treatment arms

End point title	Comparison of response rate in both treatment arms

End point description:

The response rates were reported for each treatment arm with two-sided Pearson-Clopper confidence intervals and were tested for difference using the chi-squared test.

End point type	Secondary

End point timeframe:

over the time period of 3 years

End point values	Arm A: continued 5-Azacitidine	Arm B: Allogeneic stem cell transplantation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	81		
Units: precentage	26	59		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from the time point of signed inform consent, regardless of the relationship to the treatment. All AEs were collected and documented by investigators in the eCRF. SAEs were reported within 24 hours by Investigators to Sponsor.

Adverse event reporting additional description:

Sponsor sent annual report of Serious Suspected Adverse Reaction (SSAR) to PEI + EC + Celgene GmbH (or on demand). SUSARs were sent within 15 days to PE +EC+Investigators by Sponsor (within 7 days if event is fatal or life-threatening).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Arm A : continous 5-Aza
Reporting group description: -	
Reporting group title	Arm B: allogeneic stem cell transplantation

Reporting group description: -

Serious adverse events	Arm A : continous 5-Aza	Arm B: allogeneic stem cell transplantation	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 27 (74.07%)	68 / 81 (83.95%)	
number of deaths (all causes)	16	39	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 27 (0.00%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Mitral valve disease			
subjects affected / exposed	0 / 27 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 27 (3.70%)	4 / 81 (4.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression	Additional description: including Event terms: progress of MDS, relapse, progression into RAEB-I/II, progression into CMML-2, progession into AML, relapse of AML		
subjects affected / exposed	14 / 27 (51.85%)	17 / 81 (20.99%)	
occurrences causally related to treatment / all	0 / 14	0 / 13	
deaths causally related to treatment / all	0 / 2	0 / 8	
Pyrexia			
subjects affected / exposed	0 / 27 (0.00%)	5 / 81 (6.17%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	0 / 27 (0.00%)	7 / 81 (8.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	3 / 3	
Graft versus host disease in liver			
subjects affected / exposed	0 / 27 (0.00%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 27 (0.00%)	3 / 81 (3.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 27 (0.00%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	0 / 27 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 27 (0.00%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	0 / 27 (0.00%)	4 / 81 (4.94%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cytomegalovirus infection			
subjects affected / exposed	0 / 27 (0.00%)	3 / 81 (3.70%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	1 / 27 (3.70%)	12 / 81 (14.81%)	
occurrences causally related to treatment / all	0 / 1	10 / 12	
deaths causally related to treatment / all	0 / 0	5 / 5	
Sepsis			
subjects affected / exposed	0 / 27 (0.00%)	7 / 81 (8.64%)	
occurrences causally related to treatment / all	0 / 0	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 6	
Septic shock			
subjects affected / exposed	0 / 27 (0.00%)	4 / 81 (4.94%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 4	

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

Non-serious adverse events	Arm A : continous 5-Aza	Arm B: allogeneic stem cell transplantation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 27 (92.59%)	74 / 81 (91.36%)	
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 27 (3.70%)	7 / 81 (8.64%)	
occurrences (all)	1	9	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	2 / 27 (7.41%)	6 / 81 (7.41%)	
occurrences (all)	2	6	
Leukaemia recurrent			
subjects affected / exposed	1 / 27 (3.70%)	5 / 81 (6.17%)	
occurrences (all)	1	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 27 (7.41%)	7 / 81 (8.64%)	
occurrences (all)	10	7	
Febrile neutropenia			
subjects affected / exposed	1 / 27 (3.70%)	11 / 81 (13.58%)	
occurrences (all)	1	11	
Leukopenia			
subjects affected / exposed	3 / 27 (11.11%)	3 / 81 (3.70%)	
occurrences (all)	8	3	
Neutropenia			
subjects affected / exposed	2 / 27 (7.41%)	2 / 81 (2.47%)	
occurrences (all)	4	2	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	7 / 27 (25.93%)	5 / 81 (6.17%)	
occurrences (all)	7	5	
Pyrexia			
subjects affected / exposed	1 / 27 (3.70%)	13 / 81 (16.05%)	
occurrences (all)	1	16	
Infections and infestations			

Cytomegalovirus infection			
subjects affected / exposed	0 / 27 (0.00%)	6 / 81 (7.41%)	
occurrences (all)	0	10	
Infection			
subjects affected / exposed	2 / 27 (7.41%)	5 / 81 (6.17%)	
occurrences (all)	2	9	
Pneumonia			
subjects affected / exposed	3 / 27 (11.11%)	14 / 81 (17.28%)	
occurrences (all)	3	14	
Sepsis			
subjects affected / exposed	0 / 27 (0.00%)	8 / 81 (9.88%)	
occurrences (all)	0	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2017	Changes of statistican; changes in secondary study endpoints; accrual of patients changed to 5.5 years; End of study changed to January 2019; Changes for statistical analysis: sample size estimation changed into 3 years + 112 days after study inclusion; number of patients reduced to 110 patients; Interim Analysis: efficacy interim analysis at 30-NOV-2017; changes in SAE classification (administration change only); additions on criteria to define event-free survival; Patient Information/Written Consent updated and changed to Version 04, 01.08.2013.

Notes:

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.

SAE Listing represents an extract of the main SAEs occurred in this study.

Notes: