Comparison between 5-azacytidine treatment and 5-azacytidine followed by allogeneic stem cell transplantation in elderly patients with advanced MDS according to donor availability	
Clinical Study Report Synopsis	
EudraCT-No.	2010-018467-42
Protocol-No.	VidazaAlloStudy
Version / Date	2.0 / 31-MAR-2021
Study Phase	Phase II
Study Start and Completion Date	04-JUL-2011 (first patient enrolled) – 31-JAN-2019
Sponsor	University Medical Center Hamburg-Eppendorf
Coordinating Investigator	Prof. Dr. med. Nicolaus Kröger Department of Stem Cell Transplantation University Medical Center Hamburg-Eppendorf Martinistr. 52 20246 Hamburg Germany

Signatures Page

This final synopsis of clinical study report has been approved by:

Coordinating Investigator Signature

I hereby confirm that I have read this final report and confirm that it describes the conduct and the results of the study.

Coordinating Investigator Signature

1 April 2021
Date

Krüger
Coordinating Investigator Name

Statistician Signature

I hereby confirm that I have read this final report and confirm that it describes the conduct and the results of the study.

Statistician Signature

Date

Statistician Name

CONFIDENTIAL

The study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents for at least 15 years.

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Coordinating Investigator Name	

Statistician Signature

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Hannes Buchner	01 Apr 2021
Statistician Signature	Date
Dr. Hannes Buchner	
Statistician Name	

CONFIDENTIAL

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2 SYNOPSIS

Name of Sponsor/Company: University Medical Center Hamburg-Eppendorf	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: NA	**Volume:**	
Name of Active Ingredient: Allogeneic hematopoietic stem cells	**Page:**	
Study Title	Comparison between 5 – azacytidine treatment and 5 – azacytidine followed by allogeneic stem cell transplantation in elderly patients with advanced MDS according to donor availability	
Coordinating Investigator	Prof. Dr. med. Nicolaus Kröger	
Study center	15 active study centers (2 additional centers were submitted but not initiated)	
Publication (reference)	Not applicable	
Protocol No.	VidazaAlloStudy	
EudraCT-No.	2010-018467-42	
Study Period	04-JUL-2011 (first patient enrolled) – 31-JAN-2019	
Phase of development	Phase II trial	
Primary Objective	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.	
Secondary Objectives	Comparison of “overall survival (OS)” and “event-free survival” between treatment arm “allogeneic stem cell transplantation after 5 azacytidine induction” and treatment arm “continuous 5 - azacytidine alone” over the whole study period. To assess the response rate, the event-free survival at three years, toxicity and treatment-related mortality (TRM), the impact of the Hematopoietic cell transplantation-specific comorbidity-index (HCT-CI) on outcome and the quality of life in both treatment arms. Further to analyse prognostic factors which influence survival in both arms.	
Methodology	Phase II trial comparing allogeneic stem cell transplantation with 5-azacytidine in elderly MDS patients (intermediate I with high risk cytogenetics, intermediate II or high risk: 55-70 years) according to donor availability.	
Number of subjects	Out of 190 patients, 170 were protocol eligible. 108 patients were included and assigned to one of the treatment groups (27 ContVid and 81 SCT) and 62 patients were not assigned.	

Indication	Myelodysplastic Syndrome (MDS) (intermediate II risk, high risk or intermediate I with high risk cytogenetics)
Main criteria for inclusion	• Patients with proven de novo or therapy-related MDS / CMML (white blood cells [WBC] <13 GPT/l) according to French-American-British Consensus (FAB) and risk profile according to International Prognostic Scoring System (IPSS): intermediate II-risk or high-risk or intermediate I with high-risk cytogenetic (according to IPSS, considering that IPSS, however, was not validated for therapy-related Myelodysplastic Syndrome [t-MDS]), patients with secondary AML (according to world health organization [WHO]) and blasts ≤ 30 % (= Refractory anaemia with excess of blasts in transformation (RAEB-t) according to FAB) • Previously untreated or maximal 1 cycle of 5-azacytidine (Vidaza®) • Male or Female; Age 55 – 70 years • Understand and voluntarily sign an informed consent form • Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 at study entry • Adequate renal and liver function: creatinine and bilirubine < 3 x the upper limit of normal • Sufficient cardiac function (ejection fraction > 30 %)
Test product, dose and mode of administration, batch no.	Allogeneic hematopoietic stem cells (allo-HSC), 4-8 × 10^6 CD34+/ CD45+-cells per kg of body weight (allogeneic) administered as infusion (IV), batch no. is not applicable
Duration of treatment	Immediately after registration a donor search was performed. Patients were assigned to the allogeneic stem cell transplant arm if 10/10 matched donor was found after 4 cycles of 5-azacytidine (Vidaza®) therapy. If no suitable donor was found within this time period, the patient was assigned to continuous 5-azacytidine arm (“genetic” randomization) until progression. After progression, further treatment was up to the treating physician. If the patient was assigned to allogeneic stem cell transplantation a 5th and 6th cycle of 5-azacytidine could be performed in order to prepare the patient for the transplant procedure. However, allogeneic stem cell transplantation had to be performed 4 weeks after the 6th cycle of 5-azacytidine at the latest.
Reference product, dose and mode of administration	Vidaza ® (5-Azacitidine), 75 mg/m^2 subcutaneous
Criteria for evaluation **Efficacy and Safety**	Efficacy: • Primary endpoint: Overall survival at three years between both treatment arms. • Secondary endpoints: 1. Overall survival (events being death from any cause) for all subjects assigned to one of the two treatment arms as time to event endpoint. 2. Event-free survival (events being disease progression, relapse after complete remission or partial re-

	mission, death from any cause) for all subjects assigned to one of the two treatment arms as time to event endpoint. 3. Comparison of response rate and duration according IWG response criteria in Myelodysplastic Syndrome between both treatment arms. 4. The event-free survival was assessed by three years. 5. The evaluation of toxicity was performed according to the reporting guidelines as per NCI-CTCAE. 6. Overall survival and event-free survival adjusted by the comorbidity-index (HCT-CI) according Sorror 7. Comparison of treatment-related mortality at three years. 8. Comparison of quality of life between both treatment arms according to the life core questionnaire QLQ-C30 and the treatment specific high-dose chemotherapy module QLQ HD-C29 of the EORTC Quality of Life Group. • <u>Safety endpoint:</u> Adeverse events (AEs) during the study were evaluated as a safety endpoint.
Statistical methods	The predefined interim analysis was performed on 27-FEB-2018. The complete type I error probability α was spent at the interim analysis. Therefore, no further adjustment for multiplicity was done. The primary endpoint overall survival at three years between both treatment arms was analyzed 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 representing the initial 5-aza therapy. The secondary effectiveness analyses were comparison of 'overall survival' (events being death from any cause) and event-free survival (events being disease progression, relapse after complete remission or partial remission, death from any cause) between treatment arm Hematopoietic stem cell transplantation (HSCT) and treatment arm continuous azacytidine illustrated with Kaplan-Meier estimates of survivor functions and tested using the unstratified logrank test. Secondly, 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. The treatment-related mortality rates were calculated the same way as the primary endpoint. Gray's test was used to evaluate the hypothesis of cause-specific cumulative incidence functions due to treatment–related mortality between two groups after accounting for competing risk event (non-treatment-related death). The quality of life in both treatment arms were described descriptively only because there was not enough data to perform the originally planned mixed models repeated measurements analyses. Post-hoc subgroup analyses for OS were performed by age, sex, IPSS, ECOG, and by remission status at time of stem cell transplantation. All other analyses were prespecified in the protocol and the statistical analyses plan prior to database lock.

Efficacy Results	At the final analysis, the 3-year overall survival was 50% (95% CI: 39 – 61%) in the arm for allogeneic stem cell transplantation in comparison to 32% (95% CI: 14 – 52%) in the 5-aza continuous arm (p = 0.1236). The difference at interim in overall survival at three years (3.31 years) was significant at 0.49 (95% CI: 0.36, 0.61) with a p-value of 0.0273. At the final analysis, if patients in continuous 5-aza arm who received allogeneic stem cell transplant after progression were censored at time of transplant (n = 14), the 3-year overall survival was 50% vs. 33% (p = 0.5). At the final analysis, the 3-year event-free survival was significantly higher after HSCT in comparison to continuous 5-aza therapy (34% with 95% CI: 22 – 47% after allograft and 0%, p < 0.0001). Fourteen out of the 27 patients in the continuous 5-aza arm who experienced disease progression underwent salvage HSCT with alternative HLA-mismatched donor. In a multivariate analysis for EFS including sex, ECOG, IPSS, recipients age, remission, and treatment only allogeneic stem cell transplant remains significant, HR: 0.51 (95% CI: 0.28 – 0.95, p = 0.03).
Safety Results	At the final analysis, after treatment with Vidaza (ContVid), death from all causes occurred in 16 patients (59.3%). Adverse events (AEs) occurred in 25 patients (92.6%), severe AEs occurred in 20 patients (74.1%), AE of toxicity grade III or higher occurred in 20 patients (74.1%), severe AEs of toxicity grade III or higher occurred in 11 patients (40.7%), treatment-related AEs occurred in 13 patients (48.1%), and treatment-related severe AEs occurred in 5 patients (18.5%). For the stem cell transplant arm (SCT arm), death from all causes occurred in 39 patients (48.1%), AEs occurred in 74 patients (91.4%), there were severe AEs in 68 patients (84.0%), AE of toxicity grade III or higher occurred in 66 patients (81.5%), severe AEs of toxicity grade III or higher occurred in 62 patients (76.5%),treatment-related AEs occurred in 49 patients (60.5%) , and treatment-related severe AEs occurred in 44 patients (54.3%). AEs were occurred nearly in similar number of patients in both treatment arms ContVid and SCT (92.6% and 91.4% respectively).

Conclusions	*Event-free survival (EFS)* The 3-year event-free survival was significantly higher after HSCT in comparison to continuous 5-azacytidine (Vidaza®) therapy (34% with 95% CI: 22 – 47% after allograft and 0% p < 0.0001). The results from the interim analysis are in line with the result from final analysis. Fourteen out of the 27 patients in the continuous 5-azacytidine (Vidaza®) arm who experienced disease progression underwent salvage HSCT with alternative Human leukocyte antigen (HLA)-mismatched donor. In a multivariate analysis for EFS including sex, ECOG, IPSS, recipients age, remission, and treatment only allogeneic stem cell transplant remains significant, HR:0.51 (95% CI: 0.28 -0.95, p = 0.03). *Overall survival (OS)* The 3-year overall survival was 50% (95% CI: 39 – 61%) in the arm for allogeneic stem cell transplantation in comparison to 32% (95% CI: 14 – 52%) in the Vidaza arm (p = 0.1236). If patients in the continuous 5-azacytidine (Vidaza®) arm who received allogeneic stem cell transplant after progression were censored at time of transplant (n = 14) the 3-year overall survival was 50% vs. 33% (p = 0.5). A survival benefit was mainly seen in patients > 65 years, in IPSS intermediate II, and patients in remission (PR/CR) at transplant. In a multivariate analysis for OS allogeneic stem cell transplant resulted in a HR of 0.9 (95% CI: 0.50 – 1.73, p = 0.8) and none of the included variables such as sex, ECOG, IPSS, recipients age, and remission was significant. In the current study, therapy-related mortality after 1 year was 19% for those who had a completely matched sibling or 10/10 HLA compatible unrelated donor after initial therapy with 5-aza. While there was a significant event-free survival benefit for those who received allogeneic stem cell transplantation in comparison to those who continued 5-azacytidine therapy, the study did not meet its primary endpoint of a significantly improved 3-year overall survival. In conclusion, in older MDS patients, reduced conditioning (RIC) HSCT resulted in a significantly improved EFS in comparison to continuous 5-azacytidine (Vidaza®) therapy. Bridging with continuous 5-azacytidine (Vidaza®) prior to HSCT is associated with a considerable rate of drop outs due to progression, mortality and adverse events. The high dropout rate of patients during the induction phase with azacytidine suggests, however, that timing of allogeneic stem cell transplantation is essential and probably should be done as soon as a compatible donor is available without further delay.
Date of Clinical Study Report Synopsis	31-MAR-2021

An overview of principal investigators for each study site and, if applicable, their deputies is provided in the Table below.
The listed study sites were submitted to the ethics committee according to the formerly applicable law in October 2010. During the course of the study, a revaluation for the study sites # 03 Bonn, # 06 Ulm and #10 Hannover according to the new law (“2. AMG Änderungsgesetz”) took place.

Site no.	Site	Principal investigator (EC approval status, 27.05.2011)	Changes during the course of the study	Principal Investigator (Status report 04.04.2019)	Deputy (Status report 04.04.2019)	Comment
1	Universitätsklinikum Hamburg-Eppendorf Martinistr. 52, 20246 Hamburg	Prof. Dr. Nicolaus Kröger (LKP)		Prof. Dr. Nicolaus Kröger (LKP)	N.A.	
2	Klinikum rechts der Isar III. Medizinische Klinik und Poliklinik Technische Universität München Ismaningerstr. 22, 81675 München	Dr. Helge Menzel		Dr. Helge Menzel		Site not initiated and no patients included
3	Universitätsklinikum Bonn Sigmund-Freud-Str. 25, 53105 Bonn	PD Dr. Marie v. Lilienfeld	31.05.2012 – new PI - Prof. Dr. Dominik Wolf Revaluation of the study sites according to new law: 28.03.2018 Principal investigator: Prof. Dr. Dominik Wolf Deputy: Dr. Karin Tina Mayer	Prof. Dr. Dominik Wolf	Dr. Karin Tina Mayer	
4	Universität zu Köln Kerpener Str. 62, 50937 Köln	PD Dr. Christof Scheid		Prof. Dr. Christof Scheid	N.A.	
5	Universitätsklinikum Carl Gustav Carus Fetscherstr. 74, 01307 Dresden	PD Dr. Uwe Platzbecker		Prof. Dr. Uwe Platzbecker	N.A.	
6	Universitätsklinikum Ulm Albert-Einstein-Allee 23, 89081 Ulm	PD Dr. Richard F. Schlenk	Revaluation of the study sites according to new law: 30.08.2016 – new PI - PD Dr. Jan Krönke and deputy Dr. med. Stephanie von Harsdorf 10.07.2018- new deputy Dr. Nikolaus Jahn	PD Dr. Jan Krönke	Dr. Nikolaus Jahn	
7	Universitätsklinikum Münster Albert-Schweitzer-Str. 33, 48149 Münster	PD Dr. Matthias Stelljes		Prof. Dr. Matthias Stelljes	N.A.	

8	Universitätsklinikum Mannheim Theodor-Kutzer-Ufer 1-3, 68167 Mannheim	PD Dr. Stefan A. Klein		PD Dr. Stefan Klein	N.A.	
9	Universitätsklinikum Essen Klinik für Knochenmarktransplantation Hufelandstr. 55, 45122 Essen	Prof. Dr. Dietrich W. Beelen		Prof. Dr. Dietrich Beelen	N.A.	
10	Medizinische Hochschule Hannover Carl-Neuberg-Str. 1, 30625 Hannover	Dr. Dr. Michael Stadler	Revaluation of the study sites according to new law: 28.03.2017 Principal investigator: Dr. Dr. Michael Stadler Deputy: PD Dr. Felicitas Thol	Dr. Dr. Michael Stadler	PD Dr. Felicitas Thol	
11	Klinikum Frankfurt am Main Theodor Stern Kai 7, 60590 Frankfurt (Main)	PD Dr. Gesine Bug		PD Dr. Gesine Bug	N.A.	
12	Universitätsklinikum Düsseldorf Moorenstr. 5, 40225 Düsseldorf	PD Dr. Guido Kobbe		Prof. Dr. Guido Kobbe	N.A.	
13	Medizinische Universitätsklinik II Tübingen Ottfried-Müller Str. 10, 72076 Tübingen	PD Dr. Wolfgang Bethge		Prof. Dr. Wolfgang Bethge	N.A.	
14	Charité Campus Benjamin Franklin Med. Klinik III, Hämotologie Hindenburgdamm 30, 12203 Berlin	Prof. Dr. Lutz Uharek		Prof. Dr. Lutz Uharek		Site not initiated and no patients included
15	Universitätsmedizin Göttingen Robert-Koch-Str. 40, 37075 Göttingen	Prof. Dr. Gerald Wulf		Prof. Dr. Gerald Wulf	N.A.	
16	Klinikum Nürnberg Prof. E. Nathanstraße 1, 90419 Nürnberg	Dr. Kerstin Schäfer-Eckart		Dr. Kerstin Schäfer-Eckart	N.A.	
17	Universitätsklinikum Essen Klinik für Hämatologie Hufelandstr. 55, 45147 Essen	Dr. Richard Noppeney		Dr. Richard Noppeney	N.A.	

Audit Trail

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