Clinical trial results:
Treatment of patients with MDS or AML with an impending hematological relapse with Azacitidin (Vidaza (R))

Summary

EudraCT number	2010-022388-37
Trial protocol	DE
Global end of trial date	12 February 2021

Results information

Result version number	v1 (current)
This version publication date	07 April 2023
First version publication date	07 April 2023

Trial information

Trial identification

Sponsor protocol code	TUD-RELA02-048

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01462578
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Technische Universität Dresden
Sponsor organisation address	Helmholtzstraße 10, Dresden, Germany, 01069
Public contact	coordinating investigator, MK1, Bereich Klinische Studien, Universitätsklinikum Dresden,, +49 3514582722, rela02@uniklinikum-dresden.de
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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	09 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 February 2021
Global end of trial reached?	Yes
Global end of trial date	12 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Analysis of the effectiveness of azacitidine 6 months after start of therapy to prevent a hematological relapse in MDS or AML patients with significant residuals or an increase of minimal residual disease (MRD) which is defined as
- decrease of CD34 donor chimerism (<80%) after allogeneic related or unrelated HSCT in CD34+ or CD117+ MDS or AML or
- Increase in the AML-specific molecular markers in the quantitative PCR for t(6,9), NPM1+ AML >1% (ratio to reference gene) after conventional chemotherapy or allogeneic HSCT or
- Persistence of the (above) MRD level >1% after conventional chemotherapy or allogeneic HSCT

Protection of trial subjects:

In the responsibility of the investigator, subjects were closely monitored during this study. Via the safety desk, the coordinating investigator on behalf of the sponsor reviewed all reported SAEs for reasonable suspected causal relationship to the investigational treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2011
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: 95
Worldwide total number of subjects	95
EEA total number of subjects	95

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)	62
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients aged 18 years or older with advanced MDS or AML, who had achieved a complete remission after conventional chemotherapy or allogeneic haemopoietic stem-cell transplantation.

Pre-assignment

Screening details:

Initially, a screening phase was performed. Patients could be selected at any time after allogeneic HSCT or conventional chemotherapy. The screening ended 2 years after completion of therapy (chemotherapy or allogeneic HSCT). Before any action could take place, the inclusion and exclusion criteria were checked.

Period 1

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

Arms

Arm title	Azacitidin

Arm description:

Azacitidine was applied once daily for 7 days, every 28 days (7 days of application + 21 days of rest). All patients initially received 6 cycles of azacitidine, with further dose adjustments according to MRD level after cycle 6.

Arm type	Experimental
Investigational medicinal product name	Vidaza (R)
Investigational medicinal product code	
Other name	Azacitidin
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dose: 75 mg/m² subcutaneous, day 1-7
Duration: initial 12 cycles at 28-day intervals, then 6 additional cycles at 56-day intervals or additional 12 cycles at 28-day intervals depending on MRD status; max. therapy duration 24 months

Number of subjects in period 1	Azacitidin
Started	95
Completed	53
Not completed	42
Adverse event, serious fatal	3
Consent withdrawn by subject	1
Physician decision	3
Adverse event, non-fatal	2
Lack of efficacy	33

Baseline characteristics

Reporting groups	
Reporting group title	overall trial (overall period)

Reporting group description: -

Reporting group values	overall trial (overall period)	Total	
Number of subjects	95	95	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	62	62	
From 65-84 years	33	33	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	52	52	
Male	43	43	

End points

End points reporting groups

Reporting group title	Azacitidin

Reporting group description:

Azacitidine was applied once daily for 7 days, every 28 days (7 days of application + 21 days of rest). All patients initially received 6 cycles of azacitidine, with further dose adjustments according to MRD level after cycle 6.

Primary: Rate of hematologic recurrence 6 months after initiation of azacitidine therapy

End point title	Rate of hematologic recurrence 6 months after initiation of azacitidine therapy[1]

End point description:

Two- sided 90% and 95% Clopper-Pearson confidence intervals were calculated. A one-sample binomial test at a one-sided significance level of 0.05 was conducted separately in both cohorts. The test in cohort 1 was conducted as confirmatory test, whereas the test in the second cohort was defiend as descriptive.

End point values:
Cohort 1: Estimate: 0.585; two-sided 90% exact CI: 0.463 - 0.7
Cohort 2: Estimate: 0.690; two-sided 90% exact CI: 0.554 - 0.806

End point type	Primary

End point timeframe:

The primary analysis was conducted in the FAS. Absolute and relative frequencies of patients who are alive and relapse free 6 months after start of treatment are presented.

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: further information can be found in the publication (see online references)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All adverse events, including additional illnesses, have been documented in the patient record and subsequently in the eCRF. AEs were documented from the first administration of the investigational product until 30 days after the last application.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: further information can be found in the publication (see online references)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2011	1.1: additions 1.2: revision of the visit schedule 5.1.1: addition of inclusion citeria for the screening phase 6.4: additions about the destruction of study medication 7.1 – 7.4: additions 8.2 – 8.3: additions about the documentation of AE/SAE
16 October 2013	- The inclusion criteria were modified at several positions to include the additional molecular marker CD117+. - 2.2: Explanation of the use of the CD117+ marker. - 4.5: The modalities for completion of screening and trial were specified. - 4.6: The timeline was adapted to the current status of recruitment and the end of recruitment/trial date was extended. - 5: The test population and the inclusion criteria were supplemented by the molecular marker CD117+. - 6.1: Linguistic corrections have been made. - 6.2: Side effects have been adapted (supplemented) according to the current SmPC. - 6.6: A passage was added that allows the interruption of the administration of the investigational medication on weekends/holidays for organizational reasons. - 6.7: Dose adjustment is not based on elevated leukocyte levels but on neutrophil levels. -7.1: In the future, buccal smears should also be sent to the laboratory to determine the MRD. -7.2: A note was added that the visits V 0.0 (screening/ inclusion) and V1.0 (start of treatment) should not take place on the same day. - 7.3: The passage that the interruption of the administration of the test medication on weekends/holidays is permitted for organizational reasons has also been inserted here. - 8: The chapter "Translational Research" has been completely added. - 9.1: The definition of Adverese Event was changed from "nachteiliges Vorkommnis" to "medizinisches Vorkommnis". - 9.1: The deadline for reporting events to Celgene was made more specific.

28 September 2015	- In general: In some passages, linguistic changes have been made in order to formulate the facts more clearly. Due to the newly added investigations of immunoregulatory and molecular markers and to achieve a high number of evaluable samples, the number of patients was increased to 93 patients in the treatment phase and the recruitment period was extended until December 2017. Among the inclusion criteria, molecular markers t(8;21) and inv16 were deleted. The main changes in the protocol are listed below in chronological order. - Involved persons/ institutions: Personnel changes in the Translational Research Laboratory and Study Coordination were recorded. - 1.1: The necessary examination materials in the context of the initial determination of the molecular marker were defined more precisely, depending on the previous therapy received. - 1.2: Missing visits were added, the procedure after cycle 12 and the exact duration of therapy were specified. -2.3 and 2.4: The background of additional analyses of predictive molecular markers as well as immunomodulatory regulators in translational research is described. - 4.3: Addition of the following investigations in the context of translational research were made: - Frequency of PD-1 on T cells and PD-L1 on blasts, respectively. - Mutation load of selected genes (e.g. DNMT3A, TET2) and their impact on response. - 4.4: In addition to the modulation of T and NK cells, the expression of immune regulators will be monitored under treatment with azacitidine. This will require an additional 40 ml of heparin blood and 10 ml of bone marrow from patients at the time of any hematologic relapse. - 4.5: The number of patients was increased to 93 patients in the treatment phase to achieve a sufficient number of samples for the evaluation of the additional parameters.
24 June 2016	- Involved persons/institutions: Personnel changes in the trial management as well as in the laboratory were recorded. - 5.1 and 5.1.1: Study inclusion for patients with CD34+ or CD117+ chimerism in case of allogeneic HSCT was narrowed down to CD34+/CD117+ positivity of blasts of ≥ 10%. - 6.1: The following new indication has been added to the comments on the approval of azacitidine (Vidaza®) according to the current SmPC: Treatment of adult patients 65 years of age and older with AML with > 30% bone marrow blasts who are not suitable for HSCT. - 6.2: Newly reported pyoderma gangraenosum was added to the list of adverse reactions according to the current SmPC for azacitidine (Vidaza®). The adverse reactions reported for the new patient group have also been added to the list. - 7.1: In the flowchart for the patient population qualifying for the RELAZA2 trial, the two molecular markers t(8;21) and inv16 were removed. These were already removed as inclusion criteria in the previous amendment. - 13.1 and 13.2.1: The analysis of the primary endpoint will be conducted with the first 53 treatment patients as initially planned. During the analysis, recruitment will continue to reach the patient numbers (93) for the secondary endpoint analysis. The description of the analysis methods and the further procedure after the primary hypothesis test were completed and described.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

20 August 2015	After reaching the originally planned patient number of 53 until the approval of protocol version 5, a recruitment stop occured. In protocol version 5 the patient number was increased to 93 patients.	27 November 2015

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30442503