Clinical trial results:
A randomized placebo-controlled phase 2 study of decitabine with or without eltrombopag in AML patients 65 years of age not eligible for intensive chemotherapy

Summary

EudraCT number	2014-003150-13
Trial protocol	DE
Global end of trial date	26 December 2020

Results information

Result version number	v1 (current)
This version publication date	27 June 2024
First version publication date	27 June 2024
Summary attachment (see zip file)	Clinical Study Report (DELTA_ClinicalStudyReport_1.0_20230626 final.pdf)

Trial information

Trial identification

Sponsor protocol code	TUD-DELTA1-063

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02446145
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, Coordinating investigator, MK1, Bereich Klinische Studien,, +49 3514585198, mk1-klinische-studien@ukdd.de
Scientific contact	Coordinating investigator, Coordinating Investigator, MK1, Bereich Klinische Studien,, +49 3514585198, mk1-klinische-studien@ukdd.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	26 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 December 2020
Global end of trial reached?	Yes
Global end of trial date	26 December 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess whether the addition of eltrombopag improves efficacy and tolerability of the standard treatment with hypomethylating agents in thrombocytopenic AML patients who are ≥65 years of age and nonfit for intensive chemotherapy

Protection of trial subjects:

An independent Data safety monitoring board (DSMB) was set in order to oversee the safety of the trial subjects by periodic safety assessments of the trial therapy . The DSMB followed specific guidelines outlined in the DSMB charter.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 132
Worldwide total number of subjects	132
EEA total number of subjects	132

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	120
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

Adult subjects (≥65 years of age) with newly-diagnosed AML defined by ≥20% blasts in the bone marrow or blood and not eligible for intensive induction therapy and planned therapy with DAC (decitabine) or AZA (azacitidine)

Pre-assignment

Screening details:

The screening tests outlined in the protocol are standard practice and could be conducted before obtaining consent. Patients who fulfilled the eligibility criteria for trial participation were provided with the approved patient information sheet by the investigator, allowing them to make an informed decision regarding their participation.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum

Arm description:

EPAG will be given in combination with standard-dose DAC or AZA treatment as concomitant medication

Arm type	Experimental
Investigational medicinal product name	Eltrombopag
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dose:
Starting dose 200 mg/d p.o.; escalation up to 300 mg/d p.o
East Asian patients: Starting dose 100 mg/d p.o.; escalation up to 150 mg/d p.o
Duration: cycle days 12-25 q4w (max. 12 cycles)

Concomitant medication (both treatment arms):
Treatment with standard-dose DAC
Decitabine 20 mg/m² i.v. d 1-5 q4w
or
Treatment with standard-dose AZA
Azacitidine 75 mg/m2 s.c. d 1-7 q4w

Arm title	Control

Arm description:

Placebo will be given in combination with standard-dose DAC or AZA treatment as concomitant medication

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dose: number of tablets according to Verum arm
Duration: cycle days 12-25 q4w (max. 12 cycles)

Concomitant medication (both treatment arms):
Treatment with standard-dose DAC
Decitabine 20 mg/m² i.v. d 1-5 q4w
or
Treatment with standard-dose AZA
Azacitidine 75 mg/m2 s.c. d 1-7 q4w

Number of subjects in period 1[1]	Verum	Control
Started	53	52
Completed	53	52

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In total 132 patients were enrolled, but 27 patients had to be excluded from the analysis. Exclusions included patients enrolled before protocol version 5.0 (N=19), withdrawal of consent before the first adm. of study med. (N=2), patient death before the first adm. of study med. (N=1), no adm. of study med. or placebo (N=4), and one patient whose diagnosis was changed from AML to MDS after randomization (N=1). 105 randomized patients have started treatment with Eltrombopag/Placebo.

Baseline characteristics

Reporting groups	
Reporting group title	Verum
Reporting group description:	
EPAG will be given in combination with standard-dose DAC or AZA treatment as concomitant medication	
Reporting group title	Control
Reporting group description:	
Placebo will be given in combination with standard-dose DAC or AZA treatment as concomitant medication	

Reporting group values	Verum	Control	Total
Number of subjects	53	52	105
Age categorical			
Units: Subjects			
From 65-84 years	49	47	96
85 years and over	4	5	9
Gender categorical			
Units: Subjects			
Female	20	20	40
Male	33	32	65

End points

End points reporting groups

Reporting group title	Verum
Reporting group description:	
EPAG will be given in combination with standard-dose DAC or AZA treatment as concomitant medication	
Reporting group title	Control
Reporting group description:	
Placebo will be given in combination with standard-dose DAC or AZA treatment as concomitant medication	

Primary: Treatment change-free survival (TCFS)

End point title	Treatment change-free survival (TCFS)[1]
End point description:	
TCFS is defined as time interval from day of randomisation to the day of death or until day one of the new disease modifying treatment (all chemotherapeutic and disease modifying agents except hydrea, including when given within subsequent clinical trials). For a patient who is not known to have died or changed disease modifying treatment by the end of observational period (Treatment period + follow-up period), observation of TCFS will be censored on the date the patient was last known to be alive.	
End point type	Primary
End point timeframe:	
Treatment change free survival (TCFS) defined as time from randomisation until day one of the new disease modifying treatment or death as the primary endpoint of this study	

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 attached clinical study report

End point values	Verum	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	52		
Units: Median TCFS time [months]				
number (confidence interval 95%)	4.2 (3.2 to 6.7)	4.6 (3.5 to 6.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

During the trial all adverse events CTCAE ≥ grade 3 have been documented in the eCRF. AEs needed to be documented from the date of randomisation until 28 days after the date of study termination.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

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 attached clinical study report

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 May 2016	During the trial, a significant protocol amendment took place in May 2016 for the following reasons. Despite positive results from a phase 1 trial indicating the viability and tolerance of the EPAG and AZA combination in high-risk MDS15, the subsequent placebo-controlled multi-center trial (SUPPORT trial, NCT02158936) evaluating EPAG in MDS patients with IPSS int-1/int-2/high-risk and thrombocytopenia was prematurely terminated in January 2016. Due to the data of the SUPPORT trial, we cannot exclude that these results have a direct implications for the DELTA study. Although the interim results of the SUPPORT trial are not completely transferable to the DELTA study (use of AZA, inclusion of lower-risk MDS patients) we believed that the data was strong enough to support an amendment of the DELTA study, which had recruited only a limited number of 19 patients at the time of submission. Within the SUPPORT trial, EPAG was given concomitantly to AZA therapy which might, at least partly, explain the presented results. In fact, TPO specifically activates Erk and NF-κB pathway that directly affects the double-strand break repair machinery through increased DNA-protein kinase phosphorylation and nonhomologous end-joining repair efficiency and fidelity.16;17 As a matter of fact, EPAG, when given at the same time, might alleviate the desired effects of an HMA-based therapy. Therefore, the DELTA trial was amended in two ways. 1. We changed the concomitant EPAG administration to a sequential approach with no overlap in order to omit interactions between both agents. 2. Additionally, meanwhile AZA has become available as a treatment option for elderly AML patients comparable to DAC. Therefore, the use of AZA (or DAC) was allowed within the study as well. As a consequence of the amendment, the sample size was increased by 19 patients to account for the patients which have had enroled already. Futher information can be found in the attached clinical trial report.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 May 2016	reason: supply shortage of IMP	22 September 2016
18 April 2019	reason: disagreement with the patient insurance company with regard on extension of duration of patient insurance	16 May 2019
30 June 2020	reason: insufficient recruitment due to new treatment options shown to be superior to study treatment	-

Notes:

Limitations and caveats

None reported