Clinical trial results:
Randomized comparison between two dose levels of daunorubicin and between one versus two cycles of in-duction therapy for adult patients with acute myeloid leukemia 65 years

Summary

EudraCT number	2013-003191-12
Trial protocol	DE CZ
Global end of trial date	25 April 2022

Results information

Result version number	v1 (current)
This version publication date	05 July 2024
First version publication date	05 July 2024
Summary attachment (see zip file)	2Dauno_Clinical Study Report (2DAUNO_SynopsisClinicalStudyReportICHE3_V1-0_20240209.pdf)

Trial information

Trial identification

Sponsor protocol code	TUD-2DAUNO-058

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02140242
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicalTrials.gov: NCT02140242

Notes:

Sponsors

Sponsor organisation name	Technische Universität Dresden
Sponsor organisation address	Helmholtzstraße 10, Dresden, Germany, 01069
Public contact	Prof. Dr. med. Christoph Röllig, Coordinating Principal Investigator, MK1, Bereich klinische Studien, +49 3514583965, annett.haake@ukdd.de
Scientific contact	Prof. Dr. med. Christoph Röllig, Coordinating Principal Investigator, MK1, Bereich klinische Studien, +49 3514583965, annett.haake@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	09 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2022
Global end of trial reached?	Yes
Global end of trial date	25 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Trial part I: To investigate whether a higher dose of daunorubicin in induction chemotherapy leads to an in-crease in good responders defined as having <5% myeloid blasts on day 15 after start of induction
- Trial part II: To investigate whether the rate of CR/CRi after single induction is similar to that after double induction in patients with a good response to induction I.

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	16 April 2014
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: 789
Country: Number of subjects enrolled	Czechia: 75
Worldwide total number of subjects	864
EEA total number of subjects	864

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)	864
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Newly diagnosed or secondary acute myeloid leukemia in adult patients ≤ 65 years of age.

Study inclusion occurred after the initial diagnosis of AML, the inclusion and exclusion criteria were checked and the study was included with subsequent randomization/registration.

Pre-assignment

Screening details:

Srceening examinations were done to determine the patients eligibility for the study within 7 days before
study entry.

Period 1

Period 1 title	Trial Part I
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment arm “DA90”

Arm description:

Daunorubicin 90 mg/m2 BSA infusion over 60 minutes days 3-5
Cytarabine 100 mg/m2 BSA cont. infusion over 24 hours days 1-7

The Full Analysis Set is reported. The FAS consisted of all patients that were randomised in part 1 and not excluded according to principles outlined in the ICH E9 guideline4 section 5.2.1. Deviating from the statistical analysis plan an additional ITT population was defined post-hoc to be able to analyse all patients who received their first induction within the trial. This ITT
population consists of all FAS patients (randomized) plus patients who received DA60 after the protocol amendment following the interim analysis for trial part 1 (non-randomized). After the interim analysis the DA90 arm was stopped and standard treatement was declared DA60 for all subsequent patients.

Arm type	Experimental
Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daunorubicin 90 mg/m2 BSA infusion over 60 minutes days 3-5

Arm title	Treatment arm “DA60”

Arm description:

Daunorubicin 60 mg/m2 BSA infusion over 60 minutes days 3-5
Cytarabine 100 mg/m2 BSA cont. infusion over 24 hours days 1-7

Arm type	Active comparator
Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daunorubicin 60 mg/m2 BSA infusion over 60 minutes days 3-5

Number of subjects in period 1	Treatment arm "DA90"	Treatment arm "DA60"
Started	157	707
Completed	157	707

Period 2	
Period 2 title	Trial Part II
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Treatment arm "S"

Arm description:

Single Induction: no further induction cycle

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Treatment arm "D"

Arm description:

Double Induction: second cycle of induction with DA
Patients received DA90 as first induction and received therefore DA45 as IT II:
Daunorubicin 45 mg/m2 infusion over 60 minutes days 3-5
Cytarabine 100 mg/m2 cont. infusion over 24 hours days 1-7

Patients received DA60 as first induction and received therefore DA60 as IT II:
Daunorubicin 60 mg/m2 infusion over 60 minutes days 3-5
Cytarabine 100 mg/m2 cont. infusion over 24 hours days 1-7

The Per Protocol Set is reported. The PPS consisted of all patients of the FAS that met all of the following criteria:
D15 blast count < 5% (good response after induction 1)
No second induction cycle in arm S before remission control
Second induction cycle in arm D before remission control
Application of cytarabine and daunorubicin in the second cycle of arm D
Applied doses of daunorubicine not lower than 90% and not higher than 110% of the planned doses in second cycle of arm D
--> clinical trial report

Arm type	Active comparator
Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received DA90 as first induction and received therefore DA45 as Induction therapy II:
Daunorubicin 45 mg/m2 infusion over 60 minutes days 3-5

Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received DA60 as first induction and received therefore DA60 as Induction therapy II:
Daunorubicin 60 mg/m2 infusion over 60 minutes days 3-5

Number of subjects in period 2[1]	Treatment arm "S"	Treatment arm "D"
Started	189	188
Completed	189	188

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only patients with a good response in Part I started in Period 2.
Further information can be found in the attached clinical study report

Baseline characteristics

Reporting groups

Reporting group title	Treatment arm "DA90"

Reporting group description:

Daunorubicin 90 mg/m2 BSA infusion over 60 minutes days 3-5
Cytarabine 100 mg/m2 BSA cont. infusion over 24 hours days 1-7

The Full Analysis Set is reported. The FAS consisted of all patients that were randomised in part 1 and not excluded according to principles outlined in the ICH E9 guideline4 section 5.2.1. Deviating from the statistical analysis plan an additional ITT population was defined post-hoc to be able to analyse all patients who received their first induction within the trial. This ITT
population consists of all FAS patients (randomized) plus patients who received DA60 after the protocol amendment following the interim analysis for trial part 1 (non-randomized). After the interim analysis the DA90 arm was stopped and standard treatement was declared DA60 for all subsequent patients.

Reporting group title	Treatment arm "DA60"

Reporting group description:

Daunorubicin 60 mg/m2 BSA infusion over 60 minutes days 3-5
Cytarabine 100 mg/m2 BSA cont. infusion over 24 hours days 1-7

Reporting group values	Treatment arm "DA90"	Treatment arm "DA60"	Total
Number of subjects	157	707	864
Age categorical Units: Subjects			
Adults (18-64 years)	157	707	864
Gender categorical Units: Subjects			
Female	74	324	398
Male	83	383	466

End points

End points reporting groups

Reporting group title	Treatment arm “DA90”

Reporting group description:

Daunorubicin 90 mg/m2 BSA infusion over 60 minutes days 3-5
Cytarabine 100 mg/m2 BSA cont. infusion over 24 hours days 1-7

The Full Analysis Set is reported. The FAS consisted of all patients that were randomised in part 1 and not excluded according to principles outlined in the ICH E9 guideline4 section 5.2.1. Deviating from the statistical analysis plan an additional ITT population was defined post-hoc to be able to analyse all patients who received their first induction within the trial. This ITT
population consists of all FAS patients (randomized) plus patients who received DA60 after the protocol amendment following the interim analysis for trial part 1 (non-randomized). After the interim analysis the DA90 arm was stopped and standard treatement was declared DA60 for all subsequent patients.

Reporting group title	Treatment arm “DA60”

Reporting group description:

Daunorubicin 60 mg/m2 BSA infusion over 60 minutes days 3-5
Cytarabine 100 mg/m2 BSA cont. infusion over 24 hours days 1-7

Reporting group title	Treatment arm “S”

Reporting group description:

Single Induction: no further induction cycle

Reporting group title	Treatment arm “D”

Reporting group description:

Double Induction: second cycle of induction with DA
Patients received DA90 as first induction and received therefore DA45 as IT II:
Daunorubicin 45 mg/m2 infusion over 60 minutes days 3-5
Cytarabine 100 mg/m2 cont. infusion over 24 hours days 1-7

Patients received DA60 as first induction and received therefore DA60 as IT II:
Daunorubicin 60 mg/m2 infusion over 60 minutes days 3-5
Cytarabine 100 mg/m2 cont. infusion over 24 hours days 1-7

The Per Protocol Set is reported. The PPS consisted of all patients of the FAS that met all of the following criteria:
D15 blast count < 5% (good response after induction 1)
No second induction cycle in arm S before remission control
Second induction cycle in arm D before remission control
Application of cytarabine and daunorubicin in the second cycle of arm D
Applied doses of daunorubicine not lower than 90% and not higher than 110% of the planned doses in second cycle of arm D
--> clinical trial report

Primary: Rate (percentage) of good responders two weeks after start of induction defined by the presence of <5% myeloid blasts on day 15 after start of IT

End point title	Rate (percentage) of good responders two weeks after start of induction defined by the presence of <5% myeloid blasts on day 15 after start of IT[1]

End point description:

End point type	Primary

End point timeframe:

Dichotomous endpoint: Rate of patients who achieve a good response as defined by marrow blasts <5% at early response assessment on day 15 of induction.

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: The statistical analysis is the calculation of success rates and confidence intervals and an uncorrected chi-squared test to compare these rates.
Further information can be found in the attached clinical study report

End point values	Treatment arm "DA90"	Treatment arm "DA60"		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	160		
Units: percent				
number (confidence interval 95%)	47.77 (39.75 to 55.88)	43.12 (35.33 to 51.18)		

Statistical analyses

No statistical analyses for this end point

Primary: Rate (percentage) of complete hematological remissions (CR/CRi) as defined by standard criteria [Döhner 2010] after induction treatment.

End point title	Rate (percentage) of complete hematological remissions (CR/CRi) as defined by standard criteria [Döhner 2010] after induction treatment.[2]

End point description:

End point type	Primary

End point timeframe:

Dichotomous endpoint: rate of patients who achieve a complete remission (CR/CRi, as defined by protocol) at any time point during study participation, i.e. until day 35 to 42 of last induction cycle.

Notes:

[2] - 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: A non-inferiority test according to Farrington and Manning was calculated here.
Further information can be found in the attached clinical study report

End point values	Treatment arm "S"	Treatment arm "D"		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	153		
Units: percent				
number (confidence interval 95%)	87.43 (81.59 to 91.95)	91.50 (85.91 to 95.40)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: AEs needed to be documented from signature of the informed consent until 28 days after the last dose of daunorubicin administered in the context of this trial.	
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
31 March 2017	- Randomization in trial part I suspended after results of preplanned interim analysis and offer all patients the standard dose of 60 mg/m2 daunorubicin in both induction cycles (part I and II of the trial) - Study treatment will be changed – DA90 will be removed, all patients receive the standard dose of 60mg/m2 daunorubicin (DA60) - According to low study-specific risk due to the reduced daunorubicin dose in part I of the trial, all trial-related risks have been removed from the protocol and there are no intervention-related cardiac risks associated with trial participation. Therefore, visits 2-6; 9-12 and the drop out visit are not necessary and have been removed from visit schedule. In visit 7,8 and 13, the study specific assessments (such as echocardiography, ECG, cardiac markers, bilirubine and creatinine measures) were deleted. - Inclusion age raised to 65 years based on the current German treatment guidelines in which patients up to the age of 65 are considered eligible for intensive induction chemotherapy with DA60 [Onkopedia-Leitlinie 2017] -Based on the results of interim analysis of part I of the trial, statistics were updated to reflect the changes in protocol version 5.0 (section 11.0). Protocol version 5.0 includes all amendments to the trial protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported