



## 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<br>(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 increase 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  $\leq 65$  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:

Screening 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                  |
| <b>Arm title</b>             | Treatment arm "DA90" |

Arm description:

Daunorubicin 90 mg/m<sup>2</sup> BSA infusion over 60 minutes days 3-5  
Cytarabine 100 mg/m<sup>2</sup> 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 guideline<sup>4</sup> 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 treatment 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/m<sup>2</sup> BSA infusion over 60 minutes days 3-5

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Treatment arm "DA60" |
|------------------|----------------------|

Arm description:

Daunorubicin 60 mg/m<sup>2</sup> BSA infusion over 60 minutes days 3-5  
Cytarabine 100 mg/m<sup>2</sup> 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/m<sup>2</sup> BSA infusion over 60 minutes days 3-5

| Number of subjects in period 1 | Treatment arm<br>"DA90" | Treatment arm<br>"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               |
| <b>Arm title</b>             | Treatment arm "S" |

Arm description:

Single Induction: no further induction cycle

|   |                   |
|---|-------------------|
| Arm type  | No intervention   |
| No investigational medicinal product assigned in this arm |                   |
| <b>Arm title</b>  | 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/m<sup>2</sup> infusion over 60 minutes days 3-5

Cytarabine 100 mg/m<sup>2</sup> cont. infusion over 24 hours days 1-7

Patients received DA60 as first induction and received therefore DA60 as IT II:

Daunorubicin 60 mg/m<sup>2</sup> infusion over 60 minutes days 3-5

Cytarabine 100 mg/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> infusion over 60 minutes days 3-5

| <b>Number of subjects in period 2<sup>[1]</sup></b> | 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/m<sup>2</sup> BSA infusion over 60 minutes days 3-5

Cytarabine 100 mg/m<sup>2</sup> 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 guideline<sup>4</sup> 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 treatment was declared DA60 for all subsequent patients.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Treatment arm "DA60" |
|-----------------------|----------------------|

Reporting group description:

Daunorubicin 60 mg/m<sup>2</sup> BSA infusion over 60 minutes days 3-5

Cytarabine 100 mg/m<sup>2</sup> 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:<br>Daunorubicin 90 mg/m2 BSA infusion over 60 minutes days 3-5<br>Cytarabine 100 mg/m2 BSA cont. infusion over 24 hours days 1-7<br><br>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 guideline <sup>4</sup> 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 treatment was declared DA60 for all subsequent patients.   |                      |
| Reporting group title  | Treatment arm "DA60" |
| Reporting group description:<br>Daunorubicin 60 mg/m2 BSA infusion over 60 minutes days 3-5<br>Cytarabine 100 mg/m2 BSA cont. infusion over 24 hours days 1-7  |                      |
| Reporting group title  | Treatment arm "S"    |
| Reporting group description:<br>Single Induction: no further induction cycle   |                      |
| Reporting group title  | Treatment arm "D"    |
| Reporting group description:<br>Double Induction: second cycle of induction with DA<br>Patients received DA90 as first induction and received therefore DA45 as IT II:<br>Daunorubicin 45 mg/m2 infusion over 60 minutes days 3-5<br>Cytarabine 100 mg/m2 cont. infusion over 24 hours days 1-7<br><br>Patients received DA60 as first induction and received therefore DA60 as IT II:<br>Daunorubicin 60 mg/m2 infusion over 60 minutes days 3-5<br>Cytarabine 100 mg/m2 cont. infusion over 24 hours days 1-7<br><br>The Per Protocol Set is reported. The PPS consisted of all patients of the FAS that met all of the following criteria:<br>D15 blast count < 5% (good response after induction 1)<br>No second induction cycle in arm S before remission control<br>Second induction cycle in arm D before remission control<br>Application of cytarabine and daunorubicin in the second cycle of arm D<br>Applied doses of daunorubicine not lower than 90% and not higher than 110% of the planned doses in second cycle of arm D<br>--> 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 <sup>[1]</sup> |
| End point description:  |  |
| End point type  | Primary  |
| End point timeframe:<br>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<br>"DA90"   | Treatment arm<br>"DA60"   |  |  |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type               | Reporting group           | Reporting group           |  |  |
| Number of subjects analysed      | 157                       | 160                       |  |  |
| Units: percent                   |                           |                           |  |  |
| number (confidence interval 95%) | 47.77 (39.75<br>to 55.88) | 43.12 (35.33<br>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. <sup>[2]</sup> |
|-----------------|---|

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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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 |
|-----------------|------------|

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### Dictionary used

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|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

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|                    |      |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

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

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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 | <ul style="list-style-type: none"><li>- Randomization in trial part I suspended after results of preplanned interim analysis and offer all patients the standard dose of 60 mg/m<sup>2</sup> daunorubicin in both induction cycles (part I and II of the trial)</li><li>- Study treatment will be changed – DA90 will be removed, all patients receive the standard dose of 60mg/m<sup>2</sup> daunorubicin (DA60)</li><li>- 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.</li><li>- 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]</li><li>-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.</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported