



## Clinical trial results:

**Pre-emptive therapy of acute graft versus host disease according to specific proteomic patterns after allogeneic hematopoietic stem cell transplantation.**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2008-005862-30   |
| Trial protocol           | DE               |
| Global end of trial date | 07 December 2015 |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 19 January 2024 |
| First version publication date | 19 January 2024 |

### Trial information

#### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | MHH-Pre-GvHD-001 |
|-----------------------|------------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Hannover Medical School  |
| Sponsor organisation address | Carl-Neuberg-Str. 1, Hannover, Germany, 30625  |
| Public contact               | Stabsstelle Zentrum für Klinische Forschung, Hannover Medical School, EudraCT@mh-hannover.de |
| Scientific contact           | Stabsstelle Zentrum für Klinische Forschung, Hannover Medical School, EudraCT@mh-hannover.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:

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**Results analysis stage**

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 06 October 2017  |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 07 December 2015 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 07 December 2015 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

Main objective of the trial:

To test the efficacy of pre-emptive immunosuppressive treatment (2-2.5mg prednisolone/kg BW/day) versus placebo immediately when a positive acute Graft-versus-Host disease (aGvHD, grade II-IV) and a specific proteomic pattern is observed.

Protection of trial subjects:

The clinical trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and with the standards of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). A continuous risk assessment was performed during the study.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 December 2009 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 259 |
| Worldwide total number of subjects   | 259          |
| EEA total number of subjects         | 259          |

Notes:

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**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)                      | 233 |
| From 65 to 84 years                       | 26  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

260 patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT) for hematologic malignancies or dysfunction syndromes were to be included in the clinical trial.

### Pre-assignment

Screening details:

Eligibility will be determined based upon the inclusion and exclusion criteria

### Period 1

|                              |                               |
|------------------------------|-------------------------------|
| Period 1 title               | Study period (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           |
| <b>Arm title</b>             | observational |

Arm description: -

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Placebo arm |
|------------------|-------------|

Arm description: -

|  |  |
|--|--|
| Arm type                               | Placebo  |
| Investigational medicinal product name | physiological sodium chloride solution                 |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Suspension for injection in pre-filled syringe, Tablet |
| Routes of administration               | Intravenous use, Oral use                              |

Dosage and administration details:

Treatment: 2 - 2.5 mg prednisolone/ kg BW/day or placebo (for 5 days or until clinical manifestation of aGvHD, if prior to day +5).

Taper: 1.5 mg/kg BW/ day 6-10, 1 mg/kg BW/day 11-14, 0.5 mg/kg/day 15-19 after administration

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Prednisolone |
|------------------|--------------|

Arm description: -

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Prednisolone   |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Tablet, Suspension for injection in pre-filled syringe |
| Routes of administration               | Intravenous use, Oral use                              |

Dosage and administration details:

Treatment: 2 - 2.5 mg prednisolone/ kg BW/day or placebo (for 5 days or until clinical manifestation of aGvHD, if prior to day +5).

Taper: 1.5 mg/kg BW/ day 6-10, 1 mg/kg BW/day 11-14, 0.5 mg/kg/day 15-19 after administration

| <b>Number of subjects in period 1</b> | observational | Placebo arm | Prednisolone |
|---------------------------------------|---------------|-------------|--------------|
| Started                               | 167           | 48          | 44           |
| Completed                             | 130           | 30          | 26           |
| Not completed                         | 37            | 18          | 18           |
| Consent withdrawn by subject          | 3             | 1           | 1            |
| no information                        | -             | 1           | -            |
| death                                 | 34            | 15          | 16           |
| Lost to follow-up                     | -             | -           | 1            |
| Protocol deviation                    | -             | 1           | -            |

## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | observational |
| Reporting group description: - |               |
| Reporting group title          | Placebo arm   |
| Reporting group description: - |               |
| Reporting group title          | Prednisolone  |
| Reporting group description: - |               |

| Reporting group values  | observational   | Placebo arm     | Prednisolone    |
|---|-----------------|-----------------|-----------------|
| Number of subjects  | 167             | 48              | 44              |
| Age categorical<br>Units: Subjects                                      |                 |                 |                 |
| Adults (18-64 years)<br>From 65-84 years                                |                 |                 |                 |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 49.4<br>± 14.12 | 52.9<br>± 12.64 | 53.0<br>± 11.62 |
| Gender categorical<br>Units: Subjects                                   |                 |                 |                 |
| Female<br>Male  | 59<br>108       | 21<br>27        | 15<br>29        |

| Reporting group values  | Total     |  |  |
|---|-----------|--|--|
| Number of subjects  | 259       |  |  |
| Age categorical<br>Units: Subjects                                      |           |  |  |
| Adults (18-64 years)<br>From 65-84 years                                | 0<br>0    |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -         |  |  |
| Gender categorical<br>Units: Subjects                                   |           |  |  |
| Female<br>Male  | 95<br>164 |  |  |

## End points

### End points reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | observational      |
| Reporting group description: -   |                    |
| Reporting group title  | Placebo arm        |
| Reporting group description: -   |                    |
| Reporting group title  | Prednisolone       |
| Reporting group description: -   |                    |
| Subject analysis set title   | Intention to treat |
| Subject analysis set type  | Intention-to-treat |
| Subject analysis set description:  |                    |
| all patients randomized  |                    |
| Subject analysis set title   | Per Protocol       |
| Subject analysis set type  | Per protocol       |
| Subject analysis set description:  |                    |
| all randomized patients, who fulfilled the key inclusion criteria and received double-blind treatment for at least 3 days (pre-emptive dose of $\geq 2$ mg/kg). Patients in the per-protocol population were analyzed as treated |                    |
| Subject analysis set title   | Safety             |
| Subject analysis set type  | Safety analysis    |
| Subject analysis set description:  |                    |
| patients were excluded from the safety analysis, because they didn't take any study medication   |                    |

### Primary: occurrence of aGvHD $\geq$ grade 2

|   |   |
|---|---|
| End point title   | occurrence of aGvHD $\geq$ grade 2 <sup>[1]</sup> |
| End point description:  |   |
| The primary endpoint was defined as the occurrence of aGvHD $\geq$ grade II between time of randomization and 100 days after HSCT. If a death occurs between randomization and 100 days after HSCT in a patient without aGvHD ( $\geq$ grade II), then this was also considered as treatment failure, equivalent to an aGvHD ( $\geq$ grade II).  |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| 100 days after HSCT   |   |
| Notes:  |   |
| [1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Patients who were not randomized were included into the observational study group, this group was not included in the analysis of the primary endpoint |   |

| End point values                           | Placebo arm     | Prednisolone    | Intention to treat   |  |
|--|-----------------|-----------------|----------------------|--|
| Subject group type                         | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed                | 48              | 44              | 92                   |  |
| Units: patients with aGvHD $\geq$ grade II | 12              | 11              | 23                   |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | difference between treatment groups at 100 days |
| Comparison groups          | Prednisolone v Placebo arm                      |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 92                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other <sup>[2]</sup>    |
| P-value                                 | = 1                     |
| Method                                  | Cochran-Mantel-Haenszel |

Notes:

[2] - efficacy

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Documentation of (S)AEs was done only for the duration of IMP intake (e.g. prednisolon/placebo for 19 days).

Adverse event reporting additional description:

Only number of affected subjects available, not number of events.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

|                       |              |
|-----------------------|--------------|
| Reporting group title | Prednisolone |
|-----------------------|--------------|

Reporting group description:

Prednisolone

| Serious adverse events                            | Placebo         | Prednisolone   |  |
|---|-----------------|----------------|--|
| Total subjects affected by serious adverse events |                 |                |  |
| subjects affected / exposed                       | 6 / 45 (13.33%) | 3 / 42 (7.14%) |  |
| number of deaths (all causes)                     | 1               | 0              |  |
| number of deaths resulting from adverse events    |                 |                |  |
| Blood and lymphatic system disorders              |                 |                |  |
| Pancytopenia                                      |                 |                |  |
| subjects affected / exposed                       | 1 / 45 (2.22%)  | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0          |  |
| Immune system disorders                           |                 |                |  |
| Graft versus host disease in skin                 |                 |                |  |
| subjects affected / exposed                       | 1 / 45 (2.22%)  | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0          |  |
| Pneumonia fungal                                  |                 |                |  |
| subjects affected / exposed                       | 0 / 45 (0.00%)  | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0          |  |
| Gastrointestinal disorders                        |                 |                |  |



|   |                |                |  |
|---|----------------|----------------|--|
| Diarrhoea                                       |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal haemorrhage                    |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nausea  |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Swallowing difficult                            |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vomiting  |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Pulmonary haemorrhage                           |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Oral herpes                                     |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| Hyperglycaemia                                  |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 3 %

| <b>Non-serious adverse events</b>                     | Placebo          | Prednisolone     |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 29 / 45 (64.44%) | 21 / 42 (50.00%) |  |
| Investigations  |                  |                  |  |
| C-reactive protein increased                          |                  |                  |  |
| subjects affected / exposed                           | 2 / 45 (4.44%)   | 1 / 42 (2.38%)   |  |
| occurrences (all)                                     | 2                | 1                |  |
| Congenital, familial and genetic disorders            |                  |                  |  |
| Aplasia   |                  |                  |  |
| subjects affected / exposed                           | 2 / 45 (4.44%)   | 0 / 42 (0.00%)   |  |
| occurrences (all)                                     | 2                | 0                |  |
| Nervous system disorders                              |                  |                  |  |
| Headache  |                  |                  |  |
| subjects affected / exposed                           | 2 / 45 (4.44%)   | 0 / 42 (0.00%)   |  |
| occurrences (all)                                     | 2                | 0                |  |
| General disorders and administration site conditions  |                  |                  |  |
| Mucosal inflammation                                  |                  |                  |  |
| subjects affected / exposed                           | 0 / 45 (0.00%)   | 2 / 42 (4.76%)   |  |
| occurrences (all)                                     | 0                | 2                |  |
| Oedema peripheral                                     |                  |                  |  |
| subjects affected / exposed                           | 0 / 45 (0.00%)   | 2 / 42 (4.76%)   |  |
| occurrences (all)                                     | 0                | 2                |  |
| Gastrointestinal disorders                            |                  |                  |  |
| Diarrhoea   |                  |                  |  |
| subjects affected / exposed                           | 8 / 45 (17.78%)  | 4 / 42 (9.52%)   |  |
| occurrences (all)                                     | 8                | 4                |  |
| Nausea  |                  |                  |  |
| subjects affected / exposed                           | 5 / 45 (11.11%)  | 2 / 42 (4.76%)   |  |
| occurrences (all)                                     | 5                | 2                |  |
| Vomiting  |                  |                  |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 2 / 45 (4.44%)<br>2 | 2 / 42 (4.76%)<br>2 |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)  | 1 / 45 (2.22%)<br>1 | 1 / 42 (2.38%)<br>1 |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)                | 1 / 45 (2.22%)<br>1 | 1 / 42 (2.38%)<br>1 |  |
| Renal and urinary disorders<br>Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)            | 3 / 45 (6.67%)<br>3 | 1 / 42 (2.38%)<br>1 |  |
| Cystitis haemorrhagic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 45 (0.00%)<br>0 | 3 / 42 (7.14%)<br>3 |  |
| Renal failure<br>subjects affected / exposed<br>occurrences (all)   | 1 / 45 (2.22%)<br>1 | 1 / 42 (2.38%)<br>1 |  |
| Infections and infestations<br>Bronchopulmonary aspergillosis<br>subjects affected / exposed<br>occurrences (all) | 1 / 45 (2.22%)<br>1 | 1 / 42 (2.38%)<br>1 |  |
| Candida infection<br>subjects affected / exposed<br>occurrences (all)   | 0 / 45 (0.00%)<br>0 | 2 / 42 (4.76%)<br>2 |  |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)   | 1 / 45 (2.22%)<br>1 | 1 / 42 (2.38%)<br>1 |  |
| Metabolism and nutrition disorders<br>Oedema<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 45 (4.44%)<br>2 | 0 / 42 (0.00%)<br>0 |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)  | 2 / 45 (4.44%)<br>2 | 0 / 42 (0.00%)<br>0 |  |
| Hyperglycaemia  |                     |                     |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 45 (0.00%) | 2 / 42 (4.76%) |  |
| occurrences (all)           | 0              | 2              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment          |
|-----------------|--------------------|
| 29 October 2009 | Protocol version 4 |
| 07 January 2010 | Protocol version 5 |
| 04 August 2011  | Protocol verison 6 |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33082512>