# Clinical trial results:
# The utilization of mesenchymal stem cells (MSC) for the treatment of graft versus host disease (GVHD) after allogeneic stem cell transplantation.

## Summary

| | |
|---|---|
| EudraCT number | 2013-003626-88 |
| Trial protocol | CZ |
| Global end of trial date | 17 December 2019 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 15 July 2022 |
| First version publication date | 15 July 2022 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | HOO-MSC01 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | University Hospital Pilsen |
| Sponsor organisation address | Alej Svobody 80, Pilsen, Czechia, 30460 |
| Public contact | Hematologicko-onkologické oddělení, Fakultní nemocnice Plzeň, +420 377103 722, lysak@fnplzen.cz |
| Scientific contact | Hematologicko-onkologické oddělení, Fakultní nemocnice Plzeň, 377103722 377103 722, lysak@fnplzen.cz |

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 | 31 December 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 October 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 December 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

- Determine the efficiency and safety of mesenchymal stem cells infusion in patients with steroid refractory or steroid-dependent GVHD of any type.
- Analyze changes in immunological laboratory parameters after the administration of mesenchymal stem cells.

Protection of trial subjects:

All subjects were fully informed about possible alternative therapies and had the opportunity to withdraw the informed consent at any time without affecting their further treatment. The patients were treated according to the standard procedures of the transplant center during the clinical trial. The administration of immunosuppressive drugs was not affected by the study, and the dose of corticosteroids was reduced after the achievement of clinical response (relief of GVHD). In case of insufficient MSC effect or progression of GVHD symptoms, the use of alternative immunosuppressive protocols was allowed.

Background therapy:

All patients were provided with prophylactic immunosuppressive therapy based on cyclosporine or mycophenolate mofetil. Corticosteroid therapy was indicated as first-line treatment of GVHD in all patients (acute GVHD at a dose of 0.87 (0.14 - 1.90) mg / kg / day, chronic GVHD - 0.25 (0.10 - 0, 86) mg / kg / day).

Evidence for comparator:

It was an uncontrolled single-center study. All patients enrolled in the study were treated with the advanced therapy medical product. Neither the control group withoud MSC administration nor the control group with other alternative treatment interventions were used as comparators. There were two reasons for the absence of a control group. First, the establishment of a control group would extend the period for obtaining the expected number of subjects and, in particular, the inclusion of subjects in the control arm would not be ethically correct given the available literature on the likely benefit of MSCs in the context of steroid-refractory GVHD.
Literature data available for second-line treatment of steroid-refractory GVHD were used to evaluate the efficacy, and non-inferiority of therapy with MSCs was analysed.

| | |
|---|---|
| Actual start date of recruitment | 11 March 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 6 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Czechia: 37 |
| Worldwide total number of subjects | 37 |
| EEA total number of subjects | 37 |

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) | 32 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

It was a single-center clinical trial and all patients screened for the study were treated at a single transplant center - Department of Hematology and Oncology, University Hospital Pilsen, Czech Republic. The first subject was enrolled in 3/2014, the last visit of the last enrolled subject took place in 10/2019.

### Pre-assignment

Screening details:

The main criterion for entering the study was the condition after allogeneic hematopoietic stem cell transplantation for hematological malignancy and the development of first-line treatment refractory GVHD (steroid- refractory GVHD).

### Period 1

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

### Arms

| | |
|---|---|
| **Arm title** | MSC arm |

Arm description:

Patients included into MSC arm were diagnosed with steroid-refractory or steroid-dependent GVHD after allogeneic stem cell transplantation. The participation of the subjects in the study began with the diagnosis of refractory GVHD and ended 12 months after MSC administration. The investigational medicinal product was the infusion of allogeneic mesenchymal stem cells expanded in vitro.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | mesenchymal stem cells |
| Investigational medicinal product code | not applicable |
| Other name | mesenchymal stromal cells, MSCs |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion |

Dosage and administration details:

The medicinal product was a suspension of allogeneic mesenchymal stem cells in saline and human albumin (FR 1/1 + HSA) in a dose ranging from 1.0 to 5.0 x 10e9 / kg and a volume of approximately 300 ml. The product was applied as a single infusion in most patients, a total of 38% of patients received more than one dose of MSCs (2 doses 9x, 3 doses 3x and 4 doses 3x).

| **Number of subjects in period 1** | MSC arm |
|---|---|
| Started | 37 |
| day+14 | 35 |
| day+30 | 32 |
| day+60 | 26 |
| day+100 | 25 |
| month+6 | 24 |
| Completed | 20 |
| Not completed | 17 |

| | |
|---|---|
| Adverse event, serious fatal | 16 |
| Lost to follow-up | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | overall trial |

Reporting group description: -

| Reporting group values | overall trial | Total | |
|---|---|---|---|
| Number of subjects | 37 | 37 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| age (median) | | | |
| Units: years | | | |
| median | 54 | | |
| full range (min-max) | 21 to 74 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 19 | 19 | |
| Male | 18 | 18 | |
| donor type<br>Units: Subjects | | | |
| related HLA compatible | 7 | 7 | |
| unrelated HLA compatible | 19 | 19 | |
| haploidentical | 5 | 5 | |
| unrelated mismatched | 6 | 6 | |
| primary disease | | | |
| type of primary malignant disorder | | | |
| Units: Subjects | | | |
| myeloid neoplasm | 28 | 28 | |
| lymphoid neoplasm | 9 | 9 | |
| GVHD grade | | | |
| severity of GVHD at the time of MSC infusion | | | |
| Units: Subjects | | | |
| grade I/II | 23 | 23 | |
| grade III/IV | 14 | 14 | |
| time since transplantation to MSC infusion | | | |
| median | | | |
| Units: month | | | |

| | | | |
|---|---|---|---|
| median<br>full range (min-max) | | - | |

| **Subject analysis sets** | |
|---|---|
| Subject analysis set title | acute GVHD |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description:<br>subjects with acute GVHD (two patients not included into analysis due to early death before first time point - day+14) | |
| Subject analysis set title | chronic GVHD |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description:<br>patients with chronic GVHD | |
| Subject analysis set title | day+0 lymphocyte aGVHD |
| Subject analysis set type | Per protocol |
| Subject analysis set description:<br>analysis of lymphocyte subpopulations kinetics in aGVHD patients (dy+0 vs. day+60), only patients surviving after day+60 included | |
| Subject analysis set title | day+60 lymphocyte aGVHD |
| Subject analysis set type | Per protocol |
| Subject analysis set description:<br>analysis of lymphocyte subpopulations kinetics in aGVHD patients (dy+0 vs. day+60), only patients surviving after day+60 included | |
| Subject analysis set title | day+0 lymphocyte chGVHD |
| Subject analysis set type | Per protocol |
| Subject analysis set description:<br>analysis of lymphocyte subpopulations kinetics in chGVHD patients (dy+0 vs. day+60) | |
| Subject analysis set title | day+60 lymphocyte chGVHD |
| Subject analysis set type | Per protocol |
| Subject analysis set description:<br>analysis of lymphocyte subpopulations kinetics in chGVHD patients (dy+0 vs. day+60) | |

| **Reporting group values** | acute GVHD | chronic GVHD | day+0 lymphocyte aGVHD |
|---|---|---|---|
| Number of subjects | 19 | 16 | 13 |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous | | | |
| age (median) | | | |
| Units: years | | | |

| | | | |
|---|---|---|---|
| median | 52 | 54 | |
| full range (min-max) | 21 to 69 | 33 to 65 | |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 10 | 9 | |
| Male | 9 | 7 | |
| donor type<br>Units: Subjects | | | |
| related HLA compatible | 3 | 4 | |
| unrelated HLA compatible | 8 | 10 | |
| haploidentical | 4 | 0 | |
| unrelated mismatched | 4 | 2 | |
| primary disease | | | |
| type of primary malignant disorder | | | |
| Units: Subjects | | | |
| myeloid neoplasm | 14 | 13 | |
| lymphoid neoplasm | 5 | 3 | |
| GVHD grade | | | |
| severity of GVHD at the time of MSC infusion | | | |
| Units: Subjects | | | |
| grade I/II | 8 | 14 | |
| grade III/IV | 11 | 2 | |
| time since transplantation to MSC infusion | | | |
| median | | | |
| Units: month | | | |
| median | 3 | 24 | |
| full range (min-max) | 1 to 19 | 5 to 95 | |

| **Reporting group values** | day+60 lymphocyte aGVHD | day+0 lymphocyte chGVHD | day+60 lymphocyte chGVHD |
|---|---|---|---|
| Number of subjects | 13 | 16 | 16 |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous | | | |
| age (median) | | | |
| Units: years<br>median<br>full range (min-max) | | | |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | | | |
| donor type<br>Units: Subjects | | | |
| related HLA compatible<br>unrelated HLA compatible<br>haploidentical<br>unrelated mismatched | | | |
| primary disease | | | |
| type of primary malignant disorder | | | |
| Units: Subjects | | | |
| myeloid neoplasm<br>lymphoid neoplasm | | | |
| GVHD grade | | | |
| severity of GVHD at the time of MSC infusion | | | |
| Units: Subjects | | | |
| grade I/II<br>grade III/IV | | | |
| time since transplantation to MSC infusion | | | |
| median | | | |
| Units: month<br>median<br>full range (min-max) | | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | MSC arm |
| Reporting group description: | |
| Patients included into MSC arm were diagnosed with steroid-refractory or steroid-dependent GVHD after allogeneic stem cell transplantation. The participation of the subjects in the study began with the diagnosis of refractory GVHD and ended 12 months after MSC administration. The investigational medicinal product was the infusion of allogeneic mesenchymal stem cells expanded in vitro. | |
| Subject analysis set title | acute GVHD |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| subjects with acute GVHD (two patients not included into analysis due to early death before first time point - day+14) | |
| Subject analysis set title | chronic GVHD |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| patients with chronic GVHD | |
| Subject analysis set title | day+0 lymphocyte aGVHD |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| analysis of lymphocyte subpopulations kinetics in aGVHD patients (dy+0 vs. day+60), only patients surviving after day+60 included | |
| Subject analysis set title | day+60 lymphocyte aGVHD |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| analysis of lymphocyte subpopulations kinetics in aGVHD patients (dy+0 vs. day+60), only patients surviving after day+60 included | |
| Subject analysis set title | day+0 lymphocyte chGVHD |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| analysis of lymphocyte subpopulations kinetics in chGVHD patients (dy+0 vs. day+60) | |
| Subject analysis set title | day+60 lymphocyte chGVHD |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| analysis of lymphocyte subpopulations kinetics in chGVHD patients (dy+0 vs. day+60) | |

### Primary: response up to day+100

| | |
|---|---|
| End point title | response up to day+100 |
| End point description: | |
| Response to the MSC treatment is based on the clinical symptoms, response is determined by comparison with the patient's baseline (at the time of enrollment in the clinical trial), response is defined as: CR (complete response), PR (partial response), SD (stable disease), PRG (progression) and ORR (overall response = CR + PR). | |
| End point type | Primary |
| End point timeframe: | |
| dan+14 to day+100 | |

| End point values | acute GVHD | chronic GVHD | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 16 | | |
| Units: percent | | | | |
| complete response | 50 | 6 | | |
| partial response | 40 | 39 | | |
| stable disease/progression | 10 | 55 | | |

| Attachments (see zip file) | figure1_response_day100.pdf |
|---|---|

## Statistical analyses

| Statistical analysis title | non-inferiority to historical data |
|---|---|

Statistical analysis description:

A non-inferiority test with the null hypothesis "new drug is as effective as the literature documented efficacy of standard treatment (set at 40% for aGVHD and 40% for cGVHD) was used for the analysis. An alternative hypothesis was - "new drug has a higher effectiveness than standard treatment". The non-inferiority margin was set at 5%. Standard treatment - effectiveness: 40%, non-inferiority margin: 5%.

| | |
|---|---|
| Comparison groups | acute GVHD v chronic GVHD |
| Number of subjects included in analysis | 35 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[1] |
| P-value | < 0.0001 [2] |
| Method | Chi-squared |
| Parameter estimate | relative frequency (proportion) |
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |

Notes:

[1] - New drug is not significantly worse that „gold standard" => non-inferiority test is appropriate. The clinical success is defined as CR or PR best response within 100 days of Follow-up.
[2] - H0: $p \leq p(0)-m$ H1: $p > p(0)-m$
$p(0) = 30\%$ $m = 5\%$
Statistical significance set as level alpha=2.5%.

## Primary: lymphocyte subpopulations aGVHD

| End point title | lymphocyte subpopulations aGVHD |
|---|---|

End point description:

An analysis of the development of lymphocyte subpopulations - day+0 vs. day +60 - was performed (all patients who reached a given timepoint). The subpopulations CD3+CD8+, CD3+CD4+, NK cells and B-cells were analysed.

| End point type | Primary |
|---|---|

End point timeframe:

the comparison of absolute lymphocyte counts in aGVHD: day+0 vs. day+60

| End point values | day+0 lymphocyte aGVHD | day+60 lymphocyte aGVHD | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 13 | | |
| Units: cells/microlitre | | | | |
| median (full range (min-max)) | | | | |
| CD3+/CD4+ | 31 (6 to 273) | 63 (3 to 449) | | |
| CD3+/CD8+ | 171 (10 to 1272) | 384 (6 to 1148) | | |
| NK cells | 40 (9 to 147) | 88 (10 to 272) | | |
| B cells | 7 (0 to 40) | 10 (0 to 31) | | |
| Th1 | 0.3 (0 to 16.7) | 2.1 (0.11 to 9.9) | | |
| Th2 | 0.8 (0.01 to 13.6) | 1.9 (0.1 to 11.8) | | |
| Th17 | 0.8 (0.03 to 8.9) | 1.0 (0.5 to 6.56) | | |

| Attachments (see zip file) | changes of lymphocytes |
|---|---|

**Statistical analyses**

| Statistical analysis title | lymphocyte subpopulations |
|---|---|
| Comparison groups | day+0 lymphocyte aGVHD v day+60 lymphocyte aGVHD |
| Number of subjects included in analysis | 26 |
| Analysis specification | Post-hoc |
| Analysis type | equivalence |
| P-value | ≤ 0.05 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Median difference (final values) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard deviation |

**Primary: lymphocyte subpopulations chGVHD**

| End point title | lymphocyte subpopulations chGVHD |
|---|---|

End point description:

An analysis of the development of lymphocyte subpopulations - day+0 vs. day +60 - was performed (all patients who reached a given timepoint). The subpopulations CD3+CD8+, CD3+CD4+, NK cells and B-cells were analysed.

| End point type | Primary |
|---|---|

End point timeframe:

the comparison of absolute lymphocyte counts in chGVHD: day+0 vs. day+60

| End point values | day+0 lymphocyte chGVHD | day+60 lymphocyte chGVHD | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 16 | | |
| Units: cells/microlitre | | | | |
| median (full range (min-max)) | | | | |
| CD3+/CD4+ | 420 (27 to 1228) | 476 (44 to 1414) | | |
| CD3+/CD8+ | 705 (99 to 2469) | 649 (135 to 2238) | | |
| NK cells | 212 (41 to 1153) | 187 (23 to 1026) | | |
| B cells | 69 (0 to 1135) | 100 (1 to 1328) | | |
| Th1 | 0.5 (0.02 to 38.3) | 0.9 (0 to 19.3) | | |
| Th2 | 0.5 (0.17 to 3.64) | 0.9 (0.12 to 4.2) | | |
| Th17 | 1.9 (0.53 to 38.1) | 2.3 (0 to 6.07) | | |

| Attachments (see zip file) | changes of lymphocytes |
|---|---|

**Statistical analyses**

| Statistical analysis title | lymphocyte subpopulations |
|---|---|
| Comparison groups | day+0 lymphocyte chGVHD v day+60 lymphocyte chGVHD |
| Number of subjects included in analysis | 32 |
| Analysis specification | Post-hoc |
| Analysis type | equivalence |
| P-value | ≤ 0.05 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Median difference (final values) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard deviation |

**Secondary: infusion toxicity**

| End point title | infusion toxicity |
|---|---|
| End point description: | |
| Acute toxicity associated with MSCs (fever, allergies, headaches) is monitored. | |
| End point type | Secondary |
| End point timeframe: | |
| 2 hours after insusion of MSC | |

| End point values | acute GVHD | chronic GVHD | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 16 | | |
| Units: percent | | | | |
| infusion toxicity | 0 | 0 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: corticosteroids dose

| End point title | corticosteroids dose |
|---|---|
| End point description:<br>expressed as percentage of initial dose (at the time of MSC infusion) | |
| End point type | Secondary |
| End point timeframe:<br>dan+14 to month+6 | |

| End point values | acute GVHD | chronic GVHD | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 10 | 16 | | |
| Units: percentage | | | | |
| median (full range (min-max)) | | | | |
| day+14 | 66 (30 to 100) | 100 (21 to 100) | | |
| day+30 | 50 (0 to 179) | 78 (21 to 100) | | |
| day+60 | 31 (0 to 80) | 72 (10 to 100) | | |
| day+100 | 23 (0 to 120) | 64 (17 to 100) | | |
| month+6 | 16 (8 to 77) | 57 (12 to 100) | | |

| Attachments (see zip file) | figure2_kinetics_of_corticosteroids.pdf |
|---|---|

### Statistical analyses

No statistical analyses for this end point

### Secondary: overall survival

| End point title | overall survival |
|---|---|

End point description:

percentage of aGVHD and chGVHD patients surviving 12 months after MSC infusion (probability of survival)

figure: overall survival calculated from the date of MSC insusion, median

| End point type | Secondary |
|---|---|

End point timeframe:

from infusion of MSC do mohth +12

| **End point values** | acute GVHD | chronic GVHD | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 16 | | |
| Units: percent | | | | |
| patients alive at M+12 (percentage) | 41 | 94 | | |

| **Attachments (see zip file)** | overall survival/figure3_overall_survival.pdf |
|---|---|

**Statistical analyses**

No statistical analyses for this end point

**Secondary: regulatory cells**

| End point title | regulatory cells |
|---|---|

End point description:

initial value determined as 100%, then the change from day+0 (before application) analysed and expressed as percentage change from the original value

| End point type | Secondary |
|---|---|

End point timeframe:

the comparison of regulatory cells presence from day+0 to day+60

| **End point values** | acute GVHD | chronic GVHD | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15[3] | 11[4] | | |
| Units: percent | | | | |
| CD123 + DC increase | 0 | 66 | | |
| CD123+ D decrease | 65 | 0 | | |
| FoxP3+ T cell increase | 0 | 47 | | |
| FoxP+ T cells decrease | 56 | 0 | | |

Notes:

[3] - patients alive on day+60 analysed

[4] - patients alive on day+60 analysed

| | |
|---|---|
| **Attachments (see zip file)** | changes of regulatory |

### Statistical analyses

No statistical analyses for this end point

### Secondary: quality of life

| | |
|---|---|
| End point title | quality of life |

End point description:

evaluated as the accumulation of scores for a given QoL parameter for all patients adjusted by the number of patients in a given timepoint

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

day+0 to day+100 for acute GVHD; day+0 to month+12 for chronic GVHD

| **End point values** | acute GVHD | chronic GVHD | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 13 | 16 | | |
| Units: cumulative score | | | | |
| physical well-being day+0 | 12 | 12 | | |
| physical well-being day+100 | 9 | 11 | | |
| social/family well-being day+0 | 21 | 19 | | |
| social/family well-being day+100 | 21 | 19 | | |
| emotional well-being day+0 | 10 | 11 | | |
| emotional well-being day+100 | 8 | 11 | | |
| functional well-being day+0 | 15 | 13 | | |
| functional well-being day+100 | 17 | 13 | | |

| | |
|---|---|
| **Attachments (see zip file)** | quality of life/figure5_quality_of_life.pdf |

### Statistical analyses

No statistical analyses for this end point

### Secondary: OS subgroup analysis

| | |
|---|---|
| End point title | OS subgroup analysis |

End point description:

overal survival - comparison of subgroups based on response to the treatment on day+30 (CR x PR x SD(PRG), GVHD stage (2 x 3) and corticosteroids dose reduction on day+14 (more than 50 % x less than 50 % of the initial dose), expressed as OS medians

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

12 months

| End point values | acute GVHD | chronic GVHD | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 19 | 16 | | |
| Units: months | | | | |
| response CR | 28 | 80 | | |
| response PR | 2 | 80 | | |
| response SD/PRG | 2 | 38 | | |
| stage 3 | 5 | 35 | | |
| stage (1) 2 | 19 | 26 | | |
| corticosteroids over 50 % | 14 | 14 | | |
| corticosteroids below 50% | 35 | 35 | | |

| Attachments (see zip file) | survival curves<br>survival curves |
|---|---|

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The occurrence of adverse events (AEs) was monitored during the period up to day +30 from the application of the medicinal product. Serious adverse events (SAEs) were monitored during 12 months follow-up.

Adverse event reporting additional description:

The incidence of infectious complications was monitored separately during the 12-month follow-up. All infectious complications were monitored, regardless of severity, ie some of them are documented concurrently as SAE. The reason for this methodology was a more comprehensive assessment of immunomodulatory effect of the medicinal product.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25 |

### Reporting groups

| | |
|---|---|
| Reporting group title | (S)AE all patients |

Reporting group description:

all patients treated with MSCs within the clinical trial, regardless of the type of GVHD

| **Serious adverse events** | (S)AE all patients | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 22 / 37 (59.46%) | | |
| number of deaths (all causes) | 16 | | |
| number of deaths resulting from adverse events | 15 | | |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Multi-organ disorder | | | |
| subjects affected / exposed | 10 / 37 (27.03%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 10 | | |
| Blood and lymphatic system disorders | | | |
| Haemolysis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 6 / 37 (16.22%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 4 | | |
| Pneumonia fungal | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pneumonia viral | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cystitis bacterial | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterocolitis bacterial | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | (S)AE all patients | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 9 / 37 (24.32%) | | |
| Vascular disorders | | | |
| Thrombosis | Additional description: Thrombosis with pulmonary embolism | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Oedema | Additional description: leg oedema | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Pain | Additional description: Vertebrogenic algic syndrome | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Immune system disorders | | | |
| Graft versus host disease | Additional description: recurrence of aGvHD II.stage | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |
| Renal failure | Additional description: renal insufficiency resolved afrer therapy | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---|---|---|
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 37 (2.70%)<br>1 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 10 June 2016 | In 2016, an amendment to the clinical trial protocol was approved (Amendment 01 dated 10 June 2016), which brought the following changes:<br>- repeated MSC applications in patients with suboptimal clinical response allowed (up to 4 insusions)<br>- the expected number of subjects increased to 40 - 50<br>- separate subanalysis of patients with aGVHD and chGVHD sheduled to evaluate the clinical response. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The design of the single-arm study does not allow an independent assessment of the effectiveness of MSCs; the evaluation is complicated by limited sample size and a large number of peri-transplant variables, that increase overall variability.

Notes:

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/31863261

http://www.ncbi.nlm.nih.gov/pubmed/27516191

http://www.ncbi.nlm.nih.gov/pubmed/26143146

http://www.ncbi.nlm.nih.gov/pubmed/24548911

http://www.ncbi.nlm.nih.gov/pubmed/24077235