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 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 Units: Subjects			
Female	19	19	
Male	18	18	
donor type 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 full range (min-max)		-	

Subject analysis sets	
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)	

Reporting group values	acute GVHD	chronic GVHD	day+0 lymphocyte aGVHD
Number of subjects	19	16	13
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 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 Units: Subjects			
Female	10	9	
Male	9	7	
donor type 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 Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
age (median)			
Units: years median full range (min-max)			

Gender categorical Units: Subjects			
Female Male			
donor type Units: Subjects			
related HLA compatible unrelated HLA compatible haploidentical unrelated mismatched			
primary disease			
type of primary malignant disorder			
Units: Subjects			
myeloid neoplasm lymphoid neoplasm			
GVHD grade			
severity of GVHD at the time of MSC infusion			
Units: Subjects			
grade I/II grade III/IV			
time since transplantation to MSC infusion			
median			
Units: month median 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: expressed as percentage of initial dose (at the time of MSC infusion)	
End point type	Secondary
End point timeframe: 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 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 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 subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 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: - repeated MSC applications in patients with suboptimal clinical response allowed (up to 4 insusions) - the expected number of subjects increased to 40 - 50 - 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