



Clinical trial results: Treatment of osteoarthritis with allogeneic mesenchymal cells (MSV). Summary

EudraCT number	2011-005321-51
Trial protocol	ES
Global end of trial date	15 July 2014

Results information

Result version number	v1 (current)
This version publication date	01 October 2021
First version publication date	01 October 2021

Trial information

Trial identification

Sponsor protocol code	MSV-ALLO
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Parque Científico de la Universidad de Valladolid
Sponsor organisation address	Edificio I+D, Paseo de Belén, 11, Campus Miguel Delibes, Valladolid, Spain, 47011
Public contact	Dr. Javier García-Sancho Martín, Parque Científico de la Universidad de Valladolid, +34 912948910, enrique.conde@efficeresearch.com
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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	15 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2014
Global end of trial reached?	Yes
Global end of trial date	15 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the feasibility and safety of allogeneic MSV applied by percutaneous injection in the knee joint as a treatment for osteoarthritis of the knee

Protection of trial subjects:

The study was in compliance with ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	24
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 30 patients were enrolled at 1 investigational site. 30 patients were randomized, 15 to MSV-Allo and 15 to Hyaluronic acid. All patients were treated. Patients participated between 26/07/2012 and 12/12/2012 (last follow-up).

Pre-assignment

Screening details:

IC signed; Aged ≥ 18 ; Gonarthrosis grade ≥ 2 ; Chronic painful knee mechanical properties; No local or systemic septic process; Hematological and biochemical analysis without significant alterations.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

An online randomisation service was used. Only the investigator who implant the cells were unblind to the allocation. The MSV-ALLO and Hyaluronic acid were identical and so there was no danger of study staff or participants being unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	MSV-ALLO

Arm description:

Single dose 10 ml with cellular dose: 40 millions \pm 8 millions of Mesenchymal stem cell

Arm type	Experimental
Investigational medicinal product name	MSV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraarticular use

Dosage and administration details:

Single dose 10 ml with cellular dose: 40 millions \pm 8 millions of Mesenchymal stem cell

Arm title	Hyaluronic Acid
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Arm description:

Single dose of 60 mg of Hyaluronic Acid in 3 ml of Durolane

Arm type	Active comparator
Investigational medicinal product name	Hyaluronic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraarticular use

Dosage and administration details:

Single dose of 60 mg of Hyaluronic Acid in 3 ml of Durolane

Number of subjects in period 1	MSV-ALLO	Hyaluronic Acid
Started	15	15
Completed	15	15

Baseline characteristics

Reporting groups

Reporting group title	MSV-ALLO
Reporting group description:	
Single dose 10 ml with cellular dose: 40 millions \pm 8 millions of Mesenchymal stem cell	
Reporting group title	Hyaluronic Acid
Reporting group description:	
Single dose of 60 mg of Hyaluronic Acid in 3 ml of Durolane	

Reporting group values	MSV-ALLO	Hyaluronic Acid	Total
Number of subjects	15	15	30
Age categorical			
Units: Subjects			
Adults (18-64 years)	12	12	24
From 65-84 years	3	3	6
Age continuous			
Units: years			
median	56	59	
full range (min-max)	38 to 73	51 to 64	-
Gender categorical			
Units: Subjects			
Female	7	10	17
Male	8	5	13
Previous intraarticular treatment of knee osteoarthritis			
Units: Subjects			
Yes	5	8	13
No	10	7	17
Previous oral treatment of knee osteoarthritis			
Units: Subjects			
Yes	15	14	29
No	0	1	1
Kellgren and Lawrence system			
<p>The Kellgren and Lawrence system is a common method of classifying the severity of osteoarthritis (OA) using five grades:</p> <p>Gr 0 none: definite absence of x-ray changes of OA</p> <p>Gr 1 doubtful: doubtful joint space narrowing and possible osteophytic lipping</p> <p>Gr 2 minimal: definite osteophytes and possible joint space narrowing</p> <p>Gr 3 moderate: moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends</p> <p>Gr 4 severe: large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends</p>			
Units: Subjects			
Minimal	6	6	12
Moderate	6	5	11
Severe	3	3	6
Unknown	0	1	1
Knee treated			
Units: Subjects			

Right	10	12	22
Left	5	3	8

Weight			
Units: Kg			
median	70	70	
full range (min-max)	56 to 89	55 to 83	-
Height			
Units: cm			
median	164	163	
full range (min-max)	156 to 180	145 to 176	-
Body mass index			
Units: kg/m ²			
median	25.6	27.7	
full range (min-max)	21.9 to 30.0	20.6 to 30.1	-
WOMAC index (pain)			
The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a widely used, proprietary set of standardized questionnaires to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. It can be self-administered and was developed at Western Ontario and McMaster Universities in 1982. The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68).			
Units: points			
median	42.8	50.7	
full range (min-max)	23.5 to 70.0	20.3 to 71.2	-
WOMAC index (stiffness)			
The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a widely used, proprietary set of standardized questionnaires to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. It can be self-administered and was developed at Western Ontario and McMaster Universities in 1982. The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68).			
Units: points			
median	29.5	49.5	
full range (min-max)	2.5 to 76.5	8.0 to 85.0	-
WOMAC index (Physical functioning)			
The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a widely used, proprietary set of standardized questionnaires to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. It can be self-administered and was developed at Western Ontario and McMaster Universities in 1982. The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68).			
Units: points			
median	39.2	48.3	
full range (min-max)	21.3 to 62.8	21.0 to 63.5	-
Lequesne questionnaires			
Lequesne questionnaires is a self-report questionnaire instruments for patients with knee disabilities.			
Units: points			
median	37.5	45.8	
full range (min-max)	17.0 to 66.7	12.5 to 62.5	-
Health Assessment Questionnaire			
Units: points			
median	0.5	0.8	
full range (min-max)	0.0 to 1.1	0.0 to 1.3	-
Quality of life			
SF-12 v2 questionnaire			

Units: points			
median	58.8	27.1	
full range (min-max)	27.1 to 86.4	1.3 to 58.8	-
Visual Analogue Scale			
Units: points			
median	55.0	70.0	
full range (min-max)	15.0 to 81.0	4.0 to 97.0	-

End points

End points reporting groups

Reporting group title	MSV-ALLO
Reporting group description:	
Single dose 10 ml with cellular dose: 40 millions \pm 8 millions of Mesenchymal stem cell	
Reporting group title	Hyaluronic Acid
Reporting group description:	
Single dose of 60 mg of Hyaluronic Acid in 3 ml of Durolane	

Primary: Magnetic resonance imaging changes at 12 months

End point title	Magnetic resonance imaging changes at 12 months
End point description:	
End point type	Primary
End point timeframe:	
at 12 months from administration	

End point values	MSV-ALLO	Hyaluronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12 ^[1]	15		
Units: subjects				
Improvement	10	11		
No changes	0	1		
Get worse	2	3		

Notes:

[1] - No RMI performed

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6618
Method	Chi-squared

Secondary: Magnetic resonance imaging changes at 6 months

End point title	Magnetic resonance imaging changes at 6 months
End point description:	

End point type	Secondary
End point timeframe:	
At 6 months from administration	

End point values	MSV-ALLO	Hyaluronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13 ^[2]	15		
Units: subjects				
Improvement	11	11		
No changes	2	0		
Get worse	0	4		

Notes:

[2] - 2 No RMI performed

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6546
Method	Chi-squared

Secondary: Change in WOMAC index (pain)

End point title	Change in WOMAC index (pain)
End point description:	
<p>The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a widely used, proprietary set of standardized questionnaires to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. It can be self-administered and was developed at Western Ontario and McMaster Universities in 1982. The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68).</p>	
End point type	Secondary
End point timeframe:	
At day 8, 3 months, 6 months and 12 months from administration	

End point values	MSV-ALLO	Hyaluronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: points				
arithmetic mean (standard deviation)				
Day 8	-6.96 (± 12.3)	-2.88 (± 13.8)		

3 months	-10.01 (\pm 23.7)	-4.27 (\pm 17.2)		
6 months	-13.02 (\pm 19.0)	-5.97 (\pm 12.1)		
12 months	-16.30 (\pm 23.0)	-6.36 (\pm 15.8)		

Statistical analyses

Statistical analysis title	Differences between groups at day 8
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2144
Method	ANCOVA

Statistical analysis title	Differences between groups at 3 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2368
Method	ANCOVA

Statistical analysis title	Differences between groups at 6 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1289
Method	ANCOVA

Statistical analysis title	Differences between groups at 12 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0667
Method	ANCOVA

Secondary: Change in WOMAC index (stiffness)

End point title	Change in WOMAC index (stiffness)
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End point description:

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a widely used, proprietary set of standardized questionnaires to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. It can be self-administered and was developed at Western Ontario and McMaster Universities in 1982. The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68).

End point type	Secondary
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End point timeframe:

At day 8, 3 months, 6 months and 12 months from administration

End point values	MSV-ALLO	Hyaluronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: points				
arithmetic mean (standard deviation)				
Day 8	0.37 (± 21.9)	0.13 (± 23.0)		
3 months	-4.77 (± 30.5)	-1.93 (± 25.2)		
6 months	-3.17 (± 23.8)	-2.87 (± 23.6)		
12 months	-10.67 (± 31.1)	-4.50 (± 29.5)		

Statistical analyses

Statistical analysis title	Differences between groups at day 8
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3944
Method	ANCOVA

Statistical analysis title	Differences between groups at 3 months
Comparison groups	MSV-ALLO v Hyaluronic Acid

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3039
Method	ANCOVA

Statistical analysis title	Differences between groups at 6 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4022
Method	ANCOVA

Statistical analysis title	Differences between groups at 12 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2218
Method	ANCOVA

Secondary: Change in WOMAC index (Physical functioning)

End point title	Change in WOMAC index (Physical functioning)
End point description: The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a widely used, proprietary set of standardized questionnaires to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. It can be self-administered and was developed at Western Ontario and McMaster Universities in 1982. The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68).	
End point type	Secondary
End point timeframe: At day 8, 3 months, 6 months and 12 months from administration	

End point values	MSV-ALLO	Hyaluronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: points				
arithmetic mean (standard deviation)				
Day 8	-6.60 (± 19.0)	-1.43 (± 13.1)		
3 months	-8.51 (± 22.8)	-6.46 (± 18.7)		

6 months	-14.53 (\pm 19.8)	-6.97 (\pm 20.5)		
12 months	-12.59 (\pm 23.1)	-4.26 (\pm 21.3)		

Statistical analyses

Statistical analysis title	Differences between groups at day 8
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2216
Method	ANCOVA

Statistical analysis title	Differences between groups at 3 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5188
Method	ANCOVA

Statistical analysis title	Differences between groups at 6 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1085
Method	ANCOVA

Statistical analysis title	Differences between groups at 12 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1648
Method	ANCOVA

Secondary: Change in Lequesne index

End point title	Change in Lequesne index
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End point description:

End point type	Secondary
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End point timeframe:

At day 8, 3 months, 6 months and 12 months from administration

End point values	MSV-ALLO	Hyaluronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: points				
arithmetic mean (standard deviation)				
Day 8	-3.38 (± 12.1)	-1.66 (± 9.2)		
3 months	-3.63 (± 12.4)	-5.18 (± 12.8)		
6 months	-13.95 (± 10.8)	-5.46 (± 13.4)		
12 months	-8.76 (± 12.4)	-3.13 (± 12.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Health Assessment Questionnaire

End point title	Change in Health Assessment Questionnaire
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End point description:

End point type	Secondary
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End point timeframe:

At day 8, 3 months, 6 months and 12 months from administration

End point values	MSV-ALLO	Hyaluronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: points				
arithmetic mean (standard deviation)				
Day 8	0.13 (± 0.3)	-0.13 (± 0.3)		
3 months	-0.01 (± 0.2)	-0.19 (± 0.4)		
6 months	-0.13 (± 0.2)	-0.19 (± 0.4)		
12 months	-0.07 (± 0.3)	-0.12 (± 0.5)		

Statistical analyses

Statistical analysis title	Differences between groups at day 8
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0701
Method	ANCOVA

Statistical analysis title	Differences between groups at 3 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3783
Method	ANCOVA

Statistical analysis title	Differences between groups at 6 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.699
Method	ANCOVA

Statistical analysis title	Differences between groups at 12 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9627
Method	ANCOVA

Secondary: Change in Quality of life

End point title	Change in Quality of life
End point description:	
End point type	Secondary
End point timeframe:	
At day 8, 3 months, 6 months and 12 months from administration	

End point values	MSV-ALLO	Hyaluronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: points				
arithmetic mean (standard deviation)				
Day 8	2.11 (± 14.5)	2.11 (± 14.5)		
3 months	0.12 (± 22.5)	0.39 (± 16.2)		
6 months	10.64 (± 22.8)	2.11 (± 21.2)		
12 months	5.24 (± 27.9)	2.51 (± 21.1)		

Statistical analyses

Statistical analysis title	Differences between groups at day 8
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4705
Method	ANCOVA

Statistical analysis title	Differences between groups at 3 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4603
Method	ANCOVA

Statistical analysis title	Differences between groups at 6 months
Comparison groups	MSV-ALLO v Hyaluronic Acid

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0973
Method	ANCOVA

Statistical analysis title	Differences between groups at 12 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2951
Method	ANCOVA

Secondary: Change in VAS scale

End point title	Change in VAS scale
End point description:	
End point type	Secondary
End point timeframe:	
At day 8, 3 months, 6 months and 12 months from administration	

End point values	MSV-ALLO	Hyaluronic Acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: points				
arithmetic mean (standard deviation)				
Day 8	-4.47 (± 22.4)	-1.93 (± 16.1)		
3 months	-13.67 (± 30.7)	-7.53 (± 23.6)		
6 months	-20.67 (± 29.3)	-11.93 (± 20.6)		
12 months	-21.20 (± 28.5)	-13.07 (± 21.6)		

Statistical analyses

Statistical analysis title	Differences between groups at day 8
Comparison groups	MSV-ALLO v Hyaluronic Acid

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3409
Method	ANCOVA

Statistical analysis title	Differences between groups at 3 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2831
Method	ANCOVA

Statistical analysis title	Differences between groups at 6 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1371
Method	ANCOVA

Statistical analysis title	Differences between groups at 12 months
Comparison groups	MSV-ALLO v Hyaluronic Acid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2041
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall period

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	MSV-ALLO
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Reporting group description:

Single dose 10 ml with celular dose: 40 millions \pm 8 millions of Mesenchymal stem cell

Reporting group title	Hyaluronic Acid
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Reporting group description:

Single dose of 60 mg of Hyaluronic Acid in 3 ml of Durolane

Serious adverse events	MSV-ALLO	Hyaluronic Acid	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	MSV-ALLO	Hyaluronic Acid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)	13 / 15 (86.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Neoplasms			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Surgical and medical procedures Dental implantation subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 15 (13.33%) 2	
General disorders and administration site conditions Effusion subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	0 / 15 (0.00%) 0	
Reproductive system and breast disorders Amenorrhoea subjects affected / exposed occurrences (all) Testicular pain subjects affected / exposed occurrences (all) Premature menopause subjects affected / exposed occurrences (all) Menorrhagia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0	0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 0 / 15 (0.00%) 0 2 / 15 (13.33%) 1	
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Nervousness subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 0 / 15 (0.00%) 0	0 / 15 (0.00%) 0 1 / 15 (6.67%) 1	
Nervous system disorders			

Amnesia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Migraine subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	11 / 15 (73.33%) 1	
Somnolence subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	
Eye disorders Blefaritis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Erosión corneal subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Gastrointestinal disorders Dental pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 15 (13.33%) 2	
Skin and subcutaneous tissue disorders Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	12 / 15 (80.00%) 8	11 / 15 (73.33%) 9	
Joint effusion subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 2	5 / 15 (33.33%) 4	
Back pain			

subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	2 / 15 (13.33%) 2	
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Arthritis subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3	1 / 15 (6.67%) 1	
Infections and infestations			
Ear infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	2 / 15 (13.33%) 1	
Pneumonia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Rhinitis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported