



Clinical trial results:

Skeletal muscle-derived cell implantation for the treatment of fecal incontinence: a multicenter, randomized, double-blind, placebocontrolled, parallel-group, dose-finding clinical study.

Summary

EudraCT number	2010-021463-32
Trial protocol	AT DE SE CZ GB SI BG
Global end of trial date	19 October 2016

Results information

Result version number	v1 (current)
This version publication date	11 September 2021
First version publication date	11 September 2021
Summary attachment (see zip file)	Synopsis STEFFI (Synopsis.docx)

Trial information

Trial identification

Sponsor protocol code	IC-01-02-02-007
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Innovacell Biotechnologie AG
Sponsor organisation address	Mitterweg 24, Innsbruck, Austria, 6020
Public contact	Clinical Department Innovacell, Innovacell AG, office@innovacell.com
Scientific contact	Clinical Department Innovacell, Innovacell AG, office@innovacell.com

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 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2016
Global end of trial reached?	Yes
Global end of trial date	19 October 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to find the optimal cell count for functional regeneration of the external anal sphincter.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference of Harmonisation Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2013
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	Slovenia: 16
Country: Number of subjects enrolled	Sweden: 47
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Austria: 80
Country: Number of subjects enrolled	Bulgaria: 20
Country: Number of subjects enrolled	Czechia: 36
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 78
Country: Number of subjects enrolled	Switzerland: 4
Worldwide total number of subjects	288
EEA total number of subjects	279

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)	149
From 65 to 84 years	137
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Recruitment of patients per site was not limited and was competitive across countries (9) and sites (15). Study recruitment started in November 2013 and was planned to last 4 months, actual recruitment period was 19 months. Supportive documents (poster, leaflet and newspaper publications) were developed to boost patient recruitment.

Pre-assignment

Screening details:

Patients were to be randomized in a double-blind manner in a ratio of 1:1:1 to one of the 3 treatment groups. 288 patients were screened and 251 patients were randomized. 237 patients were finally considered as ITT population.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LCC group

Arm description:

Low cell count, $5 \pm 1 \times 10^6$ autologous skeletal muscle derived cells were injected into the external anal sphincter of the patients.

Arm type	Experimental
Investigational medicinal product name	Autologous skeletal muscle-derived cells
Investigational medicinal product code	
Other name	ICEF15
Pharmaceutical forms	Suspension for injection
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

The IMP ($5 \pm 1 \times 10^6$ cells) is stored and transported in 3 x 1 mL cell transportation medium. Each dose of IMP is filled in 3 cryovials. Prior to implantation, IMP is prepared and thawed by addition of 3 x 1 mL Ringer's lactate solution. Total volume of IMP injected for implantation is 6 mL. The IMP or placebo were injected (single administration) at Day 0 (Visit 0, V0) into the external anal sphincter of each patient using a standardized, ultrasound-guided injection tool under analgo sedation (or general anaesthesia, if preferred).

Arm title	HCC group
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Arm description:

High cell count, $50 \pm 10 \times 10^6$ autologous skeletal muscle cells were injected into the external anal sphincter of the patients.

Arm type	Experimental
Investigational medicinal product name	Autologous skeletal muscle-derived cells
Investigational medicinal product code	
Other name	ICEF15
Pharmaceutical forms	Suspension for injection
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

The IMP ($50 \pm 10 \times 10^6$ aSDMC) is stored and transported in 3 x 1 mL cell transportation medium. Each dose of IMP is filled in 3 cryovials. Prior to implantation, IMP is prepared and thawed by addition of 3 x 1 mL Ringer's lactate solution. Total volume of IMP injected for implantation is 6 mL. The IMP or placebo were injected (single administration) at Day 0 (Visit 0, V0) into the external anal sphincter of each

patient using a standardized, ultrasound-guided injection tool under analgo sedation (or general anaesthesia, if preferred).

Arm title	Placebo
Arm description: Placebo, injection of cell-free suspension into to external anal sphincter of the patient.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

The placebo is stored and transported in 3 x 1 mL cell transportation medium with no cells present. Each dose of IMP is filled in 3 cryovials. Prior to implantation, IMP is prepared and thawed by addition of 3 x 1 mL Ringer's lactate solution. Total volume of IMP injected for implantation is 6 mL. The placebo were injected (single administration) at Day 0 (Visit 0, V0) into the external anal sphincter of each patient using a standardized, ultrasound-guided injection tool under analgo sedation (or general anaesthesia, if preferred).

Number of subjects in period 1^[1]	LCC group	HCC group	Placebo
Started	86	81	84
Completed	83	75	79
Not completed	3	6	5
Not exposed to cell implantation	1	-	-
Cell implantation not successful	1	3	2
Patient not exposed to cell implantation	-	3	3
No post baseline assessment available	1	-	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: From the overall 288 patients screened only 251 were randomized to the study treatment. Finally 237 were considered as ITT population which includes all randomized patients for whom cell implantation was performed, and for whom baseline and at least one post-baseline evaluation of frequency per 7 days of incontinence episodes are available

Baseline characteristics

Reporting groups

Reporting group title	LCC group
Reporting group description: Low cell count, $5 \pm 1 \times 10^6$ autologous skeletal muscle derived cells were injected into the external anal sphincter of the patients.	
Reporting group title	HCC group
Reporting group description: High cell count, $50 \pm 10 \times 10^6$ autologous skeletal muscle cells were injected into the external anal sphincter of the patients.	
Reporting group title	Placebo
Reporting group description: Placebo, injection of cell-free suspension into to external anal sphincter of the patient.	

Reporting group values	LCC group	HCC group	Placebo
Number of subjects	86	81	84
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 Units: years			
arithmetic mean	59.6	61.4	59.4
standard deviation	± 13.2	± 13.7	± 14.8
Gender categorical Units: Subjects			
Female	78	75	78
Male	8	6	6

Reporting group values	Total		
Number of subjects	251		
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)	0 0 0 0 0 0		

Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	231		
Male	20		

End points

End points reporting groups

Reporting group title	LCC group
Reporting group description: Low cell count, $5 \pm 1 \times 10^6$ autologous skeletal muscle derived cells were injected into the external anal sphincter of the patients.	
Reporting group title	HCC group
Reporting group description: High cell count, $50 \pm 10 \times 10^6$ autologous skeletal muscle cells were injected into the external anal sphincter of the patients.	
Reporting group title	Placebo
Reporting group description: Placebo, injection of cell-free suspension into to external anal sphincter of the patient.	

Primary: Absolute change IEF 6 month

End point title	Absolute change IEF 6 month
End point description: The frequency of incontinence episodes were documented by a bowel diary that was completed by the patient. In this study, the frequency of incontinence episodes was calculated as the number of incontinence episodes over a period of 4 weeks.	
End point type	Primary
End point timeframe: Change in frequency episodes at Visit 4 (from day 152 until day 179) compared to baseline Vo (day -28 to day -1), in each treatment group.	

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: IEF change				
arithmetic mean (standard deviation)	-4.3 (\pm 8.2)	-4.8 (\pm 6.8)	-3.2 (\pm 5.2)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Statistical analysis description: The difference in the change of IE frequency per 7 days from baseline to V4 between treatment groups was investigated within a hierarchical test procedure using a one-sided Wilcoxon rank-sum test (SAS® PROC NPAR1WAY) with an alpha-level of 2.5% for each step.	
Comparison groups	LCC group v Placebo

Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1116 ^[1]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Variability estimate	Standard deviation

Notes:

[1] - Threshold for significance at 0.025 level.

Statistical analysis title	HCC versus placebo
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Statistical analysis description:

The difference in the change of IE frequency per 7 days from baseline to V4 between treatment groups was investigated within a hierarchical test procedure using a one-sided Wilcoxon rank-sum test (SAS® PROC NPAR1WAY) with an alpha-level of 2.5% for each step.

Comparison groups	Placebo v HCC group
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0175 ^[2]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Variability estimate	Standard deviation

Notes:

[2] - Threshold for significance at 0.025

Secondary: Absolute change IEF 1 month

End point title	Absolute change IEF 1 month
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End point description:

The frequency of incontinence episodes were documented by a bowel diary that was completed by the patient. In this study, the frequency of incontinence episodes was calculated as the number of incontinence episodes over a period of 4 weeks.

End point type	Secondary
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End point timeframe:

Change in frequency of incontinence episodes (from day 1 to day 28) compared to the baseline period (day -28 to day -1), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: Absolute IEF change				
arithmetic mean (standard deviation)	-3.4 (± 6)	-3.8 (± 6.9)	-1.9 (± 3.8)	

Statistical analyses

Secondary: Absolute change IEF 3 month

End point title	Absolute change IEF 3 month
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End point description:

The frequency of incontinence episodes were documented by a bowel diary that was completed by the patient. In this study, the frequency of incontinence episodes was calculated as the number of incontinence episodes over a period of 4 weeks.

End point type	Secondary
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End point timeframe:

Change in frequency of incontinence episodes (from day 62 until day 89) compared to the baseline period (day -28 to day -1), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: Absolute change IEF				
arithmetic mean (standard deviation)	-4.3 (± 7.3)	-4.5 (± 6.9)	-2.7 (± 4.8)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.271 ^[3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - Alpha level 5%

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.065 ^[4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - Alpha level 5%

Secondary: Absolute change IEF 12 months

End point title	Absolute change IEF 12 months
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End point description:

The frequency of incontinence episodes were documented by a bowel diary that was completed by the

patient. In this study, the frequency of incontinence episodes was calculated as the number of incontinence episodes over a period of 4 weeks.

End point type	Secondary
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End point timeframe:

Change in frequency of incontinence episodes (from day 332 to day 359) compared to the baseline period (day -28 to day -1), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: Absolute IEF change				
arithmetic mean (standard deviation)	-3.8 (\pm 6.6)	-5.5 (\pm 10.9)	-2.6 (\pm 5.1)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.459 ^[5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Alpha level 5%

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.203
Method	Wilcoxon (Mann-Whitney)

Secondary: Absolute change in Wexner Score 3 months

End point title	Absolute change in Wexner Score 3 months
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End point description:

Symptoms of FI were graded using Wexner's classification (including type of incontinence, pad usage, lifestyle). Wexner's scores vary between 0, normal continence, and 20, total incontinence.

End point type	Secondary
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End point timeframe:

Change in the Wexner score at day 90 compared to baseline considered as Screening (day -92), in each treatment group

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: Change in Wexner Score				
arithmetic mean (standard deviation)	-4.7 (± 5.7)	-4.9 (± 5.1)	-4.1 (± 5.3)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.479 ^[6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - Alpha level 5%

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.227 ^[7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - Alpha level 5%

Secondary: Absolute change in Wexner Score 6 months

End point title	Absolute change in Wexner Score 6 months
End point description:	Symptoms of FI were graded using Wexner's classification (including type of incontinence, pad usage, lifestyle). Wexner's scores vary between 0, normal continence, and 20, total incontinence.
End point type	Secondary

End point timeframe:

Change in the Wexner score at day 180 compared to baseline considered as Screening (day -92), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: absolute change Wexner Score				
arithmetic mean (standard deviation)	-4.6 (± 5.7)	-5.4 (± 5.5)	-5.3 (± 6.0)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.588 ^[8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - Alpha level 5%

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.869 ^[9]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - Alpha level 5%

Secondary: Absolute change visual analogue scale (VAS) 3 months

End point title	Absolute change visual analogue scale (VAS) 3 months
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End point description:

The individual perception of FI complaints will be evaluated by each patient using a standardized VAS. The VAS is an instrument that measures a characteristic or attitude believed to range across a continuum of values and cannot easily be directly measured. It is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient should mark the VAS with a vertical line representing his perception of the individual FI status. In this study, the two endpoints of the VAS are defined as "no complaints at all" (0 mm) and "worst complaints imaginable" (100 mm).

End point type	Secondary
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End point timeframe:

Change in the Visual Analogue Scale (VAS) at day 90 compared to baseline (day 0), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: cm				
arithmetic mean (standard deviation)	-1.3 (± 2.1)	-1.1 (± 2.1)	-1.0 (± 1.7)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.361 ^[10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - Alpha level of 5%

Statistical analysis title	HCC versus placebo
Comparison groups	Placebo v HCC group
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.28 ^[11]
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - Alpha level 5%

Secondary: Absolute change visual analogue scale (VAS) 6 months

End point title	Absolute change visual analogue scale (VAS) 6 months
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End point description:

The individual perception of FI complaints will be evaluated by each patient using a standardized VAS. The VAS is an instrument that measures a characteristic or attitude believed to range across a continuum of values and cannot easily be directly measured. It is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient should mark the VAS with a vertical line representing his perception of the individual FI status. In this study, the two endpoints of the VAS are defined as "no complaints at all" (0 mm) and "worst complaints imaginable" (100 mm).

End point type	Secondary
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End point timeframe:

Change in the Visual Analogue Scale (VAS) at day 180 compared to baseline (day 0), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: cm				
arithmetic mean (standard deviation)	-1.1 (± 2.3)	-1.3 (± 2.2)	-1.2 (± 2.0)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.678 ^[12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[12] - Alpha level 5%

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.665 ^[13]
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - Alpha level of 5%

Secondary: Absolute change visual analogue scale (VAS) 12 months

End point title	Absolute change visual analogue scale (VAS) 12 months
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End point description:

The individual perception of FI complaints will be evaluated by each patient using a standardized VAS. The VAS is an instrument that measures a characteristic or attitude believed to range across a continuum of values and cannot easily be directly measured. It is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient should mark the VAS with a vertical line representing his perception of the individual FI status. In this study, the two endpoints of the VAS are defined as "no complaints at all" (0 mm) and "worst complaints imaginable" (100 mm).

End point type	Secondary
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End point timeframe:

Change in the Visual Analogue Scale (VAS) at day 360 compared to baseline (day 0), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: cm				
arithmetic mean (standard deviation)	-1.2 (± 2.6)	-1.7 (± 2.6)	-1.0 (± 1.9)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.547 ^[14]
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - Alpha level 5%

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.356 ^[15]
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - Alpha level 5%

Secondary: Incontinence Episode Frequency Reduction >= 50% (1 month)

End point title	Incontinence Episode Frequency Reduction >= 50% (1 month)
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End point description:

End point type	Secondary
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End point timeframe:

Frequency of response measured as a reduction of the frequency of incontinence episodes by more than 50% under treatment (from day 1 until day 28) compared to the baseline period (day -28 to day -1) , in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: number of patients	22	20	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Incontinence Episode Frequency Reduction \geq 50% (3 months)

End point title	Incontinence Episode Frequency Reduction \geq 50% (3 months)
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End point description:

End point type	Secondary
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End point timeframe:

Frequency of response measured as a reduction of the frequency of incontinence episodes by more than 50% under treatment (from day 62 to day 89) compared to the baseline period (day -28 to day -1) , in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: number of patients	35	34	28	

Statistical analyses

No statistical analyses for this end point

Secondary: Incontinence Episode Frequency Reduction \geq 50% (6 months)

End point title	Incontinence Episode Frequency Reduction \geq 50% (6 months)
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End point description:

End point type	Secondary
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End point timeframe:

Frequency of response measured as a reduction of the frequency of incontinence episodes by more than 50% under treatment (from day 152 to day 179) compared to the baseline period (day -28 to day -1) , in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: number of patients	41	37	34	

Statistical analyses

No statistical analyses for this end point

Secondary: Incontinence Episode Frequency Reduction \geq 50% (12 months)

End point title	Incontinence Episode Frequency Reduction \geq 50% (12 months)
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End point description:

End point type	Secondary
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End point timeframe:

Frequency of response measured as a reduction of the frequency of incontinence episodes by more than 50% under treatment (from day 332 to day 359) compared to the baseline period (day -28 to day -1) , in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	74	77	
Units: number of patients	39	40	31	

Statistical analyses

No statistical analyses for this end point

Secondary: Remission rate 3 months

End point title	Remission rate 3 months
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End point description:

End point type	Secondary
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End point timeframe:

Frequency of patients in remission (remission = less than 3 incontinence episodes frequency during the 28 days period preceding V3, day 62 to day 89)

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: number of patients	28	27	29	

Statistical analyses

No statistical analyses for this end point

Secondary: Remission rate 6 months

End point title	Remission rate 6 months
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End point description:

End point type	Secondary
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End point timeframe:

Frequency of patients in remission (remission = less than 3 incontinence episodes frequency during the 28 days period preceding V4 (day 152 to day 179)

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: number of patients	32	31	34	

Statistical analyses

No statistical analyses for this end point

Secondary: Remission rate 12 months

End point title	Remission rate 12 months
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End point description:

End point type	Secondary
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End point timeframe:

Frequency of patients in remission (remission = less than 3 incontinence episodes frequency during the 28 days period preceding V5 (from day 332 to day 359).

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	75	79	
Units: number of patients in remission	30	31	28	

Statistical analyses

No statistical analyses for this end point

Secondary: Anorectal Manometry (absolute change of length of the anal canal)

End point title	Anorectal Manometry (absolute change of length of the anal canal)
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End point description:

The manometric evaluation before and after cell implantation enables measurement of the maximal and mean resting and squeeze pressures of the anal sphincter and the length of the anal canal. A low resting pressure indicates a dysfunction of the internal anal sphincter, whereas a low voluntary squeeze pressure indicates an external anal sphincter dysfunction.

End point type	Secondary
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End point timeframe:

Changes in the anorectal manometry data at day 180 compared to baseline (considered as screening, day-92), in each treatment group

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	74	79	
Units: mm				
arithmetic mean (standard deviation)	0.9 (± 5.1)	0.4 (± 5.4)	0.7 (± 6.6)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.701
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.856
Method	Wilcoxon (Mann-Whitney)

Secondary: Anorectal Manometry (absolute change resting pressure)

End point title	Anorectal Manometry (absolute change resting pressure)
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End point description:

The manometric evaluation before and after cell implantation enables measurement of the maximal and mean resting and squeeze pressures of the anal sphincter and the length of the anal canal. A low resting pressure indicates a dysfunction of the internal anal sphincter, whereas a low voluntary squeeze pressure indicates an external anal sphincter dysfunction.

End point type	Secondary
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End point timeframe:

Changes in the anorectal manometry data at day 180 compared to baseline (considered as screening, day-92), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	74	78	
Units: mmHg				
arithmetic mean (standard deviation)	1.9 (± 21.6)	-1.8 (± 20.5)	-6.3 (± 17.3)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009 ^[16]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - Alpha level 2.5%

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.176
Method	Wilcoxon (Mann-Whitney)

Secondary: Anorectal Manometry (absolute change maximum squeeze pressure)

End point title	Anorectal Manometry (absolute change maximum squeeze pressure)
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End point description:

The manometric evaluation before and after cell implantation enables measurement of the maximal and mean resting and squeeze pressures of the anal sphincter and the length of the anal canal. A low resting pressure indicates a dysfunction of the internal anal sphincter, whereas a low voluntary squeeze pressure indicates an external anal sphincter dysfunction.

End point type	Secondary
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End point timeframe:

Changes in the anorectal manometry data at day 180 compared to baseline (considered as screening, day-92), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	74	78	
Units: mmHg				
arithmetic mean (standard deviation)	1.1 (± 51.6)	-0.3 (± 40.0)	3.6 (± 41.2)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.282
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.599
Method	Wilcoxon (Mann-Whitney)

Secondary: Anorectal Manometry (absolute change first sensation)

End point title	Anorectal Manometry (absolute change first sensation)
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End point description:

The manometric evaluation before and after cell implantation enables measurement of the maximal and mean resting and squeeze pressures of the anal sphincter and the length of the anal canal. A low resting pressure indicates a dysfunction of the internal anal sphincter, whereas a low voluntary squeeze pressure indicates an external anal sphincter dysfunction.

End point type	Secondary
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End point timeframe:

Changes in the anorectal manometry data at day 180 compared to baseline (considered as screening, day-92), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	74	78	
Units: ml				
arithmetic mean (standard deviation)	13.8 (± 31.8)	9.7 (± 36.1)	10.9 (± 30.3)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.685
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.605
Method	Wilcoxon (Mann-Whitney)

Secondary: Anorectal Manometry (absolute change desire to defacate)

End point title	Anorectal Manometry (absolute change desire to defacate)
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End point description:

The manometric evaluation before and after cell implantation enables measurement of the maximal and mean resting and squeeze pressures of the anal sphincter and the length of the anal canal. A low resting pressure indicates a dysfunction of the internal anal sphincter, whereas a low voluntary squeeze pressure indicates an external anal sphincter dysfunction.

End point type	Secondary
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End point timeframe:

Changes in the anorectal manometry data at day 180 compared to baseline (considered as screening, day-92), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	74	76	
Units: ml				
arithmetic mean (standard deviation)	21.3 (± 46.6)	19.9 (± 38.5)	17.8 (± 42.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Anorectal Manometry (absolute change urgency to defacate)

End point title	Anorectal Manometry (absolute change urgency to defacate)
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End point description:

The manometric evaluation before and after cell implantation enables measurement of the maximal and mean resting and squeeze pressures of the anal sphincter and the length of the anal canal. A low resting pressure indicates a dysfunction of the internal anal sphincter, whereas a low voluntary squeeze pressure indicates an external anal sphincter dysfunction.

End point type	Secondary
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End point timeframe:

Changes in the anorectal manometry data at day 180 compared to baseline (considered as screening, day-92), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	71	75	
Units: ml				
arithmetic mean (standard deviation)	25.7 (± 47.0)	22.6 (± 55.0)	19.3 (± 52.3)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.248
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.531
Method	Wilcoxon (Mann-Whitney)

Secondary: Anorectal Manometry (absolute change maximum tolerable volume)

End point title	Anorectal Manometry (absolute change maximum tolerable volume)
End point description: The manometric evaluation before and after cell implantation enables measurement of the maximal and mean resting and squeeze pressures of the anal sphincter and the length of the anal canal. A low resting pressure indicates a dysfunction of the internal anal sphincter, whereas a low voluntary squeeze pressure indicates an external anal sphincter dysfunction.	
End point type	Secondary
End point timeframe: Changes in the anorectal manometry data at day 180 compared to baseline (considered as screening, day-92), in each treatment group.	

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	65	70	
Units: ml				
arithmetic mean (standard deviation)	32.5 (± 50.8)	28.2 (± 54.5)	17.6 (± 59.7)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.068
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.244
Method	Wilcoxon (Mann-Whitney)

Secondary: FI Quality of Life (absolute change lifestyle subscale score) 3 months

End point title	FI Quality of Life (absolute change lifestyle subscale score) 3 months
End point description: The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).	
End point type	Secondary
End point timeframe: Change of Patient's assessment based on the Quality of life questionnaire (QoL) lifestyle score (from day 62 until day 89) compared to the baseline period (day -28 to day -1).	

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	74	79	
Units: Lifestyle subscale score				
arithmetic mean (standard deviation)	0.5 (± 0.6)	0.4 (± 0.7)	0.4 (± 0.7)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.487
Method	t-test, 1-sided

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.568
Method	Wilcoxon (Mann-Whitney)

Secondary: FI Quality of Life (absolute change lifestyle subscale score) 6 months

End point title	FI Quality of Life (absolute change lifestyle subscale score) 6 months
End point description: The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).	
End point type	Secondary
End point timeframe: Change of Patient's assessment based on the Quality of life questionnaire (QoL) lifestyle score at day 180 compared to baseline considered at Screening (day -92), in each treatment group.	

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	74	79	
Units: Lifestyle subscale score				
arithmetic mean (standard deviation)	0.6 (\pm 0.7)	0.5 (\pm 0.7)	0.5 (\pm 0.7)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.69
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.702
Method	Wilcoxon (Mann-Whitney)

Secondary: FI Quality of Life (absolute change lifestyle subscale score) 12 months

End point title	FI Quality of Life (absolute change lifestyle subscale score) 12 months
End point description: The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).	
End point type	Secondary
End point timeframe: Change of Patient's assessment based on the Quality of life questionnaire (QoL) lifestyle score at day 360 compared to baseline considered at Screening (day -92), in each treatment group.	

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	55	55	
Units: Lifestyle subscale score				
arithmetic mean (standard deviation)	0.5 (\pm 0.8)	0.6 (\pm 0.8)	0.4 (\pm 0.6)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	Placebo v LCC group
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.311
Method	t-test, 1-sided

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.266
Method	Wilcoxon (Mann-Whitney)

Secondary: FI Quality of Life (absolute change coping/behavior score) 3 months

End point title	FI Quality of Life (absolute change coping/behavior score) 3 months
End point description: The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).	
End point type	Secondary
End point timeframe: Change of Patient's assessment based on the Quality of life questionnaire (QoL) coping/behavior score (from day 62 until day 89) compared to the baseline period (day -28 to day -1).	

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	74	79	
Units: coping/behavior subscale score				
arithmetic mean (standard deviation)	0.5 (\pm 0.7)	0.6 (\pm 0.7)	0.6 (\pm 0.7)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.425
Method	Wilcoxon (Mann-Whitney)

Secondary: FI Quality of Life (absolute change coping/behavior score) 6 months

End point title	FI Quality of Life (absolute change coping/behavior score) 6 months
End point description: The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).	
End point type	Secondary
End point timeframe: Change of Patient's assessment based on the Quality of life questionnaire (QoL) coping/behavior score at day 180 compared to baseline considered at Screening (day -92), in each treatment group.	

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	74	79	
Units: coping/behavior subscale score				
arithmetic mean (standard deviation)	0.6 (\pm 0.7)	0.7 (\pm 0.7)	0.6 (\pm 0.7)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.577
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.262
Method	Wilcoxon (Mann-Whitney)

Secondary: FI Quality of Life (absolute change coping/behavior score) 12 months

End point title	FI Quality of Life (absolute change coping/behavior score) 12 months
End point description: The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).	
End point type	Secondary
End point timeframe: Change of Patient's assessment based on the Quality of life questionnaire (QoL) coping/behavior score at day 360 compared to baseline considered at Screening (day -92), in each treatment group.	

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	55	55	
Units: Coping/behavior subscale score				
arithmetic mean (standard deviation)	0.5 (\pm 0.7)	0.7 (\pm 0.8)	0.5 (\pm 0.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: FI Quality of Life (absolute change depression/self-perception) 3 months

End point title	FI Quality of Life (absolute change depression/self-perception) 3 months
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End point description:

The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).

End point type	Secondary
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End point timeframe:

Change of Patient's assessment based on the Quality of life questionnaire (QoL) depression/self-perception score (from day 62 until day 89) compared to the baseline period (day -28 to day -1).

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	74	76	
Units: Depression subscale score				
arithmetic mean (standard deviation)	0.4 (\pm 0.7)	0.4 (\pm 0.7)	0.4 (\pm 0.7)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.528
Method	t-test, 1-sided

Statistical analysis title	HCC versus placebo
Comparison groups	Placebo v HCC group

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.943
Method	t-test, 1-sided

Secondary: FI Quality of Life (absolute change depression/self-perception) 6 months

End point title	FI Quality of Life (absolute change depression/self-perception) 6 months
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End point description:

The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).

End point type	Secondary
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End point timeframe:

Change of Patient's assessment based on the Quality of life questionnaire (QoL) depression/self-perception score at day 180 compared to baseline considered at Screening (day -92), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	74	77	
Units: Depression subscale score				
arithmetic mean (standard deviation)	0.5 (± 0.7)	0.5 (± 0.7)	0.4 (± 0.7)	

Statistical analyses

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.838
Method	t-test, 1-sided

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.545
Method	t-test, 1-sided

Secondary: FI Quality of Life (absolute change depression/self-perception) 12 months

End point title	FI Quality of Life (absolute change depression/self-perception) 12 months
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End point description:

The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).

End point type	Secondary
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End point timeframe:

Change of Patient's assessment based on the Quality of life questionnaire (QoL) depression / self-perception score at day 360 compared to baseline considered at Screening (day -92), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	55	54	
Units: Depression subscale score				
arithmetic mean (standard deviation)	0.3 (± 0.8)	0.3 (± 0.6)	0.4 (± 0.7)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.441
Method	t-test, 1-sided

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo

Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.54
Method	Wilcoxon (Mann-Whitney)

Secondary: FI Quality of Life (absolute change embarrassment) 3 months

End point title	FI Quality of Life (absolute change embarrassment) 3 months
End point description: The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).	
End point type	Secondary
End point timeframe: Change of Patient's assessment based on the Quality of life questionnaire (QoL) embarrassment score (from day 62 until day 89) compared to the baseline period (day -28 to day -1).	

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	74	79	
Units: Embarrassment subscale score				
arithmetic mean (standard deviation)	0.6 (± 0.8)	0.7 (± 0.8)	0.6 (± 0.8)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.671
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.715
Method	Wilcoxon (Mann-Whitney)

Secondary: FI Quality of Life (absolute change embarrassment) 6 months

End point title	FI Quality of Life (absolute change embarrassment) 6 months
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End point description:

The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).

End point type	Secondary
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End point timeframe:

Change of Patient's assessment based on the Quality of life questionnaire (QoL) embarrassment score at day 180 compared to baseline considered at Screening (day -92), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	74	79	
Units: Embarrassment subscale score				
arithmetic mean (standard deviation)	0.6 (± 0.8)	0.8 (± 0.9)	0.7 (± 0.9)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.436
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.685
Method	Wilcoxon (Mann-Whitney)

Secondary: FI Quality of Life (absolute change embarrassment) 12 months

End point title	FI Quality of Life (absolute change embarrassment) 12 months
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End point description:

The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).

End point type	Secondary
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End point timeframe:

Change of Patient's assessment based on the Quality of life questionnaire (QoL) embarrassment score at day 332 compared to baseline considered at Screening (day -92), in each treatment group.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	55	55	
Units: Embarrassment subscale score				
arithmetic mean (standard deviation)	0.5 (± 0.7)	0.9 (± 1.0)	0.5 (± 0.8)	

Statistical analyses

Statistical analysis title	LCC versus placebo
Comparison groups	LCC group v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.818
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HCC versus placebo
Comparison groups	HCC group v Placebo

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.156
Method	Wilcoxon (Mann-Whitney)

Secondary: FI Quality of Life (absolute change total score)

End point title	FI Quality of Life (absolute change total score)
End point description: The patients' health-related QoL before and after cell implantation will be assessed using the Rockwood Fecal Incontinence Quality of Life Scale. This validated QoL scale was developed to address issues specifically related to FI. It consists of 29 items with questions regarding the following areas of impact: lifestyle (10 items), coping/behavior (9 items), depression/self-perception (7 items), and embarrassment (3 items).	
End point type	Secondary
End point timeframe: 6 months post implantation	

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	74	77	
Units: total score				
arithmetic mean (standard deviation)	2.3 (± 2.5)	2.6 (± 2.6)	2.3 (± 2.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) improvement (very much improved)

End point title	Clinical Global Impression (CGI) improvement (very much improved)
End point description: Improvement of fecal incontinence was assessed using the Clinical Global Impression scale, which is a standardized assessment tool that allow the physician to rate the severity of illness, change over time and efficiency of treatment, taking into account the patients' clinical condition and the severity of side effects. The CGI scale is widely used in clinical studies as an outcome measure.	
End point type	Secondary
End point timeframe: Investigator's assessment by the Clinical Global Impression (CGI-I) score at day 180.	

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	74	79	
Units: number of patients	14	12	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) improvement (much improved)

End point title	Clinical Global Impression (CGI) improvement (much improved)
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End point description:

Improvement of fecal incontinence was assessed using the Clinical Global Impression scale, which is a standardized assessment tool that allow the physician to rate the severity of illness, change over time and efficiency of treatment, taking into account the patients' clinical condition and the severity of side effects. The CGI scale is widely used in clinical studies as an outcome measure.

End point type	Secondary
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End point timeframe:

Investigator's assessment by the Clinical Global Impression (CGI-I) score at day 180.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	74	79	
Units: number of patients	21	23	22	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) improvement (minimally improved)

End point title	Clinical Global Impression (CGI) improvement (minimally improved)
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End point description:

Improvement of fecal incontinence was assessed using the Clinical Global Impression scale, which is a standardized assessment tool that allow the physician to rate the severity of illness, change over time and efficiency of treatment, taking into account the patients' clinical condition and the severity of side effects. The CGI scale is widely used in clinical studies as an outcome measure.

End point type	Secondary
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End point timeframe:

Investigator's assessment by the Clinical Global Impression (CGI-I) score at day 180.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	75	79	
Units: number of patients	10	10	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) improvement (no change)

End point title	Clinical Global Impression (CGI) improvement (no change)
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End point description:

Improvement of fecal incontinence was assessed using the Clinical Global Impression scale, which is a standardized assessment tool that allow the physician to rate the severity of illness, change over time and efficiency of treatment, taking into account the patients' clinical condition and the severity of side effects. The CGI scale is widely used in clinical studies as an outcome measure.

End point type	Secondary
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End point timeframe:

Investigator's assessment by the Clinical Global Impression (CGI-I) score at day 180.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	74	79	
Units: number of patients	35	27	33	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) improvement (minimally worse)

End point title	Clinical Global Impression (CGI) improvement (minimally worse)
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End point description:

End point type	Secondary
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End point timeframe:

6 months post implantation

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	74	79	
Units: number of patients	1	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) improvement (much worse)

End point title	Clinical Global Impression (CGI) improvement (much worse)
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End point description:

Improvement of fecal incontinence was assessed using the Clinical Global Impression scale, which is a standardized assessment tool that allow the physician to rate the severity of illness, change over time and efficiency of treatment, taking into account the patients' clinical condition and the severity of side effects. The CGI scale is widely used in clinical studies as an outcome measure.

End point type	Secondary
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End point timeframe:

Investigator's assessment by the Clinical Global Impression (CGI-I) score at day 180.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	74	79	
Units: number of patients	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) improvement (very much improved)

End point title	Clinical Global Impression (CGI) improvement (very much improved)
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End point description:

Improvement of fecal incontinence was assessed using the Clinical Global Impression scale, which is a standardized assessment tool that allow the physician to rate the severity of illness, change over time and efficiency of treatment, taking into account the patients' clinical condition and the severity of side effects. The CGI scale is widely used in clinical studies as an outcome measure.

End point type	Secondary
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End point timeframe:

Investigator's assessment by the Clinical Global Impression (CGI-I) score at day 360.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	56	57	
Units: number of patients	10	14	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) improvement (much improved)

End point title	Clinical Global Impression (CGI) improvement (much improved)
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End point description:

Improvement of fecal incontinence was assessed using the Clinical Global Impression scale, which is a standardized assessment tool that allow the physician to rate the severity of illness, change over time and efficiency of treatment, taking into account the patients' clinical condition and the severity of side effects. The CGI scale is widely used in clinical studies as an outcome measure.

End point type	Secondary
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End point timeframe:

Investigator's assessment by the Clinical Global Impression (CGI-I) score at day 360.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	56	57	
Units: number of patients	14	16	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) improvement (minimally improved)

End point title	Clinical Global Impression (CGI) improvement (minimally improved)
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End point description:

Improvement of fecal incontinence was assessed using the Clinical Global Impression scale, which is a standardized assessment tool that allow the physician to rate the severity of illness, change over time and efficiency of treatment, taking into account the patients' clinical condition and the severity of side effects. The CGI scale is widely used in clinical studies as an outcome measure.

End point type	Secondary
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End point timeframe:

Investigator's assessment by the Clinical Global Impression (CGI-I) score at day 360.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	56	57	
Units: number of patients	10	8	11	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) improvement (no change)

End point title	Clinical Global Impression (CGI) improvement (no change)
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End point description:

Improvement of fecal incontinence was assessed using the Clinical Global Impression scale, which is a standardized assessment tool that allow the physician to rate the severity of illness, change over time and efficiency of treatment, taking into account the patients' clinical condition and the severity of side effects. The CGI scale is widely used in clinical studies as an outcome measure.

End point type	Secondary
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End point timeframe:

Investigator's assessment by the Clinical Global Impression (CGI-I) score at day 360.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	56	57	
Units: number of patients	21	14	23	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) improvement (minimally worse)

End point title	Clinical Global Impression (CGI) improvement (minimally worse)
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End point description:

Improvement of fecal incontinence was assessed using the Clinical Global Impression scale, which is a standardized assessment tool that allow the physician to rate the severity of illness, change over time and efficiency of treatment, taking into account the patients' clinical condition and the severity of side effects. The CGI scale is widely used in clinical studies as an outcome measure.

End point type	Secondary
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End point timeframe:

Investigator's assessment by the Clinical Global Impression (CGI-I) score at day 360.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	56	57	
Units: number of patients	3	3	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) improvement (much worse)

End point title	Clinical Global Impression (CGI) improvement (much worse)
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End point description:

Improvement of fecal incontinence was assessed using the Clinical Global Impression scale, which is a standardized assessment tool that allow the physician to rate the severity of illness, change over time and efficiency of treatment, taking into account the patients' clinical condition and the severity of side effects. The CGI scale is widely used in clinical studies as an outcome measure.

End point type	Secondary
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End point timeframe:

Investigator's assessment by the Clinical Global Impression (CGI-I) score at day 360.

End point values	LCC group	HCC group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	75	79	
Units: number of patients	3	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

27 November 2013 to 19 October 2016

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

288 patients compose the safety set. 44 patients of the safety set did not receive any treatment and 37 thereof were not randomized.

Reporting group title	LCC group
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Reporting group description:

288 patients compose the safety set. 44 patients of the safety set did not receive any treatment and 37 thereof were not randomized.

Reporting group title	HCC group
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Reporting group description:

288 patients compose the safety set. 44 patients of the safety set did not receive any treatment and 37 thereof were not randomized.

Serious adverse events	Placebo	LCC group	HCC group
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 81 (4.94%)	7 / 87 (8.05%)	7 / 76 (9.21%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer stage I, with cancer in situ			
subjects affected / exposed	0 / 81 (0.00%)	1 / 87 (1.15%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 81 (0.00%)	1 / 87 (1.15%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			

subjects affected / exposed	0 / 81 (0.00%)	1 / 87 (1.15%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			
subjects affected / exposed	0 / 81 (0.00%)	0 / 87 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Exposure during pregnancy			
subjects affected / exposed	1 / 81 (1.23%)	2 / 87 (2.30%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 81 (0.00%)	0 / 87 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 81 (0.00%)	1 / 87 (1.15%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 81 (0.00%)	0 / 87 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 81 (0.00%)	1 / 87 (1.15%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric injury			
subjects affected / exposed	0 / 81 (0.00%)	0 / 87 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			

Dolichocolon			
subjects affected / exposed	0 / 81 (0.00%)	1 / 87 (1.15%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 87 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 81 (1.23%)	0 / 87 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 81 (1.23%)	0 / 87 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 81 (0.00%)	1 / 87 (1.15%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 81 (1.23%)	0 / 87 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 81 (0.00%)	1 / 87 (1.15%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Hiatus hernia			

subjects affected / exposed	0 / 81 (0.00%)	0 / 87 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 81 (0.00%)	1 / 87 (1.15%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic haematoma			
subjects affected / exposed	0 / 81 (0.00%)	0 / 87 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 87 (1.15%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	LCC group	HCC group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 81 (61.73%)	62 / 87 (71.26%)	43 / 76 (56.58%)
Investigations			
Investigations			
subjects affected / exposed	2 / 81 (2.47%)	6 / 87 (6.90%)	4 / 76 (5.26%)
occurrences (all)	12	12	12
Injury, poisoning and procedural complications			
Injury, poisoning and preceudural complications			
subjects affected / exposed	5 / 81 (6.17%)	5 / 87 (5.75%)	8 / 76 (10.53%)
occurrences (all)	18	18	18
Vascular disorders			

Vascular disorders subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 13	4 / 87 (4.60%) 13	6 / 76 (7.89%) 13
Surgical and medical procedures Surgical and medical procedures subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 3	4 / 87 (4.60%) 4	5 / 76 (6.58%) 5
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 14	2 / 87 (2.30%) 14	7 / 76 (9.21%) 14
General disorders and administration site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	6 / 87 (6.90%) 6	2 / 76 (2.63%) 2
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 17 2 / 81 (2.47%) 10	7 / 87 (8.05%) 17 5 / 87 (5.75%) 10	5 / 76 (6.58%) 17 3 / 76 (3.95%) 10
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	4 / 81 (4.94%) 4	5 / 87 (5.75%) 5	1 / 76 (1.32%) 1
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 3	5 / 87 (5.75%) 5	3 / 76 (3.95%) 3
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorder subjects affected / exposed occurrences (all)	8 / 81 (9.88%) 26	8 / 87 (9.20%) 26	10 / 76 (13.16%) 26
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	10 / 81 (12.35%)	10 / 87 (11.49%)	10 / 76 (13.16%)
occurrences (all)	30	30	30
Urinary tract infection			
subjects affected / exposed	5 / 81 (6.17%)	1 / 87 (1.15%)	2 / 76 (2.63%)
occurrences (all)	8	8	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2012	<ul style="list-style-type: none"> • Replacement of CRO • The study duration per patient was increased from 12 months to 24 months • The cell therapy doses were modified for both LCC and HCC groups. For LCC group, the dose was changed to $5 \pm 1 \times 10^6$ cells instead of $30 \pm 10 \times 10^6$ cells. For HCC group, the dose was changed to $50 \pm 10 \times 10^6$ cells instead of $90 \pm 20 \times 10^6$ cells. • Standardized pelvic muscle electrical stimulation was deleted from the protocol and the 3D sonography was added. • Adding of exclusion criteria: overlap repair and associated early atrophy of external anal sphincter, recurrent anal fistula disease, chronic diarrhea and disease or conditions (fever and/or diarrhea of unknown reasons (4 weeks), HAV (4 months), toxoplasmosis (6 months), osteomyelitis, Qfever, rheumatic fever, tuberculosis, or Salmonella) which has not been resolved within a timeframe prior to screening. Patients with positive results in bacteriological testing at visit-1 (Salmonella (Typhus), F. tularensis (Tularaemia), M. leprae (Leprosy), Brucella, Rickettsia) was added as an interim exclusion criterion. • The primary endpoint "incontinence episodes frequency, IEF" was changed for "Changes in IEF occurred under treatment (from baseline until day 180) compared to the baseline period (day -28 to day 0), in each treatment group". • An independent, unblinded Safety Board was established by the Sponsor to periodically review the total incidence of AEs and deaths in the study. • The condition for performing the second implantation with the optimal cell count offered to patients of the placebo group was detailed
14 June 2013	<ul style="list-style-type: none"> • The recruitment period duration was extended from 4 months to 12 months. • Pelvic floor electrical stimulation was added as study procedure to rehabilitate and strengthen the pelvic floor muscles. Consequently, contraindications for the use of the electro stimulation device were added as exclusion criteria. • The condition for performing the second implantation with the optimal cell count was extended to patients from the LCC group. • Supportive documents (poster, leaflet and newspaper publications) were developed to boost patient recruitment.
25 February 2014	<ul style="list-style-type: none"> • The mention "with external anal sphincter weakness or sphincter damage" was deleted from the indication "Fecal incontinence (FI) in female and male patients". • Several inclusion and exclusion criteria were clarified (reworded) and two new exclusion criteria were added: "Patients with chemotherapy related neuropathy of the bowel and pelvis" and "Patients with chronic constipation and/or overflow incontinence". • Since the efficacy of the ATIMP was not expected in a short delay after the implantation of aSMDC, the assessment period of the primary endpoint was reviewed and adapted: "Changes in frequency of incontinence episodes at V4 (from day 152 until day 179) compared to baseline V0 (day -28 to day -1), in each treatment group". The secondary endpoints were also modified accordingly. • The completion of Short Form-36 by the patients participating in the PharmacoEconomics study was added to allow a rough QALY calculation and primitive pricing analysis.

15 April 2015	<ul style="list-style-type: none"> • The follow-up period was extended. A follow-up period of 18 additional months after Visit 4 (i.e. up to 24 months post-implantation) was to be offered to the patient at Visit 4 through a specific informed consent form. The purpose of this additional follow-up period was to provide efficacy and safety data on a long-term follow-up. This follow-up period included two on-site visits at 6 months (Visit 5) and 18 months (Visit 6) after Visit 4. The secondary endpoints were modified accordingly. • The exclusion criteria about pregnancy was restricted until Visit 4 to allow patients to become pregnant during the follow-up period if they wished to. • The mention "with external anal sphincter weakness or sphincter damage" were reintroduced in the indication fecal incontinence as it better described the population selected for the study.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported