



## Clinical trial results:

**A multicenter, randomized, double-blinded, parallel-group, placebocontrolled study to assess the efficacy and safety of skeletal muscle-derived cell implantation in female patients with stress urinary incontinence**

### Summary

EudraCT number	2010-021871-10
Trial protocol	DE CZ BG AT IT GB
Global end of trial date	09 September 2015

### Results information

Result version number	v1 (current)
This version publication date	14 July 2023
First version publication date	14 July 2023

### Trial information

#### Trial identification

Sponsor protocol code	IC-01-01-05-004
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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	N/A, Innovacell AG, 0043 512573680, office@innovacell.com
Scientific contact	N/A, Innovacell AG, 0043 6765184115, 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	10 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2015
Global end of trial reached?	Yes
Global end of trial date	09 September 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective is to show superiority of skeletal muscle-derived cells (SMDCs) over placebo in female patients with SUI

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 August 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	Romania: 145
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Bulgaria: 248
Country: Number of subjects enrolled	Czechia: 34
Country: Number of subjects enrolled	Germany: 42
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	476
EEA total number of subjects	474

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)	476
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Approximately 29 centers were targeted to be involved in DE, AT, RO, BG, CZ, and UK in conducting the study. Finally 31 centers had participated in the recruitment of patients.

### Pre-assignment

Screening details:

The study was a multinational, multicenter, randomized, double-blind, placebo-controlled study with parallel-group design.

Patients were randomized in a double-blind manner to one of the following groups: Cell group or Placebo group in a ratio of 2:1 (cell group: placebo group).

476 patients were screened and 377 patients were randomized.

### 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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The randomization of patients to one of the two treatment groups was done via an Interactive Voice Response System (IVRS), which assigned the respective unique randomization number to each patient. The IVRS was furthermore used for emergency unblinding, management of IMP shipments as well as for re-ordering of biopsy transportation kits.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

cell-free medium

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Placebo, injection of cell-free suspension into to external urethral sphincter.

<b>Arm title</b>	SMDC
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Arm description:

cell therapy 0.2 x 10<sup>6</sup> cells / 2 mL, injected into the external urethral sphincter

Arm type	Experimental
Investigational medicinal product name	Skeletal muscle-derived cells (SMDCs)
Investigational medicinal product code	ICES13
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.2 x 10<sup>6</sup> cells / 2 mL SMDCs injected into the external urethral sphincter

Number of subjects in period 1 <sup>[1]</sup>	Placebo	SMDC
Started	125	252
Completed	113	235
Not completed	12	17
Consent withdrawn by subject	12	17

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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: 99 patients were screen failures and did not undergo randomization.

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description: cell-free medium	
Reporting group title	SMDC
Reporting group description: cell therapy 0.2 x 10e6 cells / 2 mL, injected into the external urethral sphincter	

Reporting group values	Placebo	SMDC	Total
Number of subjects	125	252	377
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	55.8	54.7	
standard deviation	± 11.6	± 11.2	-
Gender categorical Units: Subjects			
Female	125	252	377
Male	0	0	0

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: cell-free medium	
Reporting group title	SMDC
Reporting group description: cell therapy 0.2 x 10e6 cells / 2 mL, injected into the external urethral sphincter	

### Primary: IEF reduction response (75% reduction)

End point title	IEF reduction response (75% reduction)
End point description: Response was defined as a reduction in the incontinence episode frequency (IEF) of 75% from baseline (Visit 0) to Visit 4. The IEF was calculated as the number of incontinence episodes that occurred during 7 days preceding a visit.	
End point type	Primary
End point timeframe: 12 months post implantation	

End point values	Placebo	SMDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	243		
Units: number of patients	33	37		

### Statistical analyses

Statistical analysis title	Difference between placebo and SMDCs
Statistical analysis description: Response was defined as a reduction in the incontinence episode frequency (IEF) of 75% from baseline (Visit 0) to Visit 4. The IEF was calculated as the number of incontinence episodes that occurred during 7 days preceding a visit.	
Comparison groups	Placebo v SMDC
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.263 <sup>[1]</sup>
Method	Fisher exact
Parameter estimate	Mean difference (net)
Variability estimate	Standard deviation

Notes:

[1] - Threshold for significance at 0.025 level.

**Primary: I-QoL total score**

End point title	I-QoL total score
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End point description:

End point type	Primary
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End point timeframe:

12 months post implantation

End point values	Placebo	SMDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114 <sup>[2]</sup>	243 <sup>[3]</sup>		
Units: Improvement total score				
arithmetic mean (standard deviation)	26.13 (± 25.14)	26.35 (± 25.18)		

Notes:

[2] - 12 months post implantation data only available for 114 patients

[3] - 12 months post implantation data only available for 243 patients

**Statistical analyses**

Statistical analysis title	Difference between placebo and SMDCs
Comparison groups	Placebo v SMDC
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47 <sup>[4]</sup>
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)

Notes:

[4] - Threshold for significance at 0.025 level

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs have been collected from study start (first patient in) to 12 months post implantation. Serious Adverse Events have been collected for up to 24 months post implantation.

Adverse event reporting additional description:

377 patients were randomized within the study. The safety set includes 369 patients. Patients that were randomized but no biopsy or cell implantation has been performed were excluded from the safety set. For non serious adverse event reporting only procedure related AEs are shown below.

Assessment type	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	SMDC
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	SMDC	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 247 (4.45%)	10 / 122 (8.20%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thymoma			
subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Marginal zone B cell lymphoma			
subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			

subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	0 / 247 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture Lumbar Vertebra			
subjects affected / exposed	0 / 247 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug dispensed to wrong patient			
subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 247 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Lumbosacral radiculitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			

subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral nerve paresis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast haematoma			
subjects affected / exposed	2 / 247 (0.81%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Painful defecation			
subjects affected / exposed	0 / 247 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 247 (0.00%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Sigmadiverticulitis			
subjects affected / exposed	2 / 247 (0.81%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative intramuscular abdominal wall infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abszess vaginal lips			
subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	SMDC	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 247 (4.05%)	10 / 122 (8.20%)	
Investigations			
Bacterial test positive			
subjects affected / exposed	2 / 247 (0.81%)	0 / 122 (0.00%)	
occurrences (all)	2	0	
C-reactive protein increased			
subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Procedural pain	Additional description: Implantation or biopsy related		
subjects affected / exposed	2 / 247 (0.81%)	2 / 122 (1.64%)	
occurrences (all)	2	2	
Urinary retention postoperative			
subjects affected / exposed	1 / 247 (0.40%)	0 / 122 (0.00%)	
occurrences (all)	1	0	
Procedural hypotension			

subjects affected / exposed occurrences (all)	1 / 247 (0.40%) 1	0 / 122 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 247 (0.00%) 0	1 / 122 (0.82%) 1	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)  Puncture site pain subjects affected / exposed occurrences (all)	0 / 247 (0.00%) 0  1 / 247 (0.40%) 1	2 / 122 (1.64%) 2  0 / 122 (0.00%) 0	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)  Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 247 (0.40%) 1  1 / 247 (0.40%) 1	2 / 122 (1.64%) 2  0 / 122 (0.00%) 0	
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	1 / 247 (0.40%) 1	0 / 122 (0.00%) 0	
Renal and urinary disorders Urethral disorder subjects affected / exposed occurrences (all)  Blood urine present subjects affected / exposed occurrences (all)  Dysuria subjects affected / exposed occurrences (all)  Stress urinary incontinence	0 / 247 (0.00%) 0  0 / 247 (0.00%) 0  4 / 247 (1.62%) 4	1 / 122 (0.82%) 1  1 / 122 (0.82%) 1  0 / 122 (0.00%) 0	
Additional description: worsening of symptoms			

subjects affected / exposed occurrences (all)	1 / 247 (0.40%) 1	0 / 122 (0.00%) 0	
Nephrolithiasis subjects affected / exposed occurrences (all)	1 / 247 (0.40%) 1	0 / 122 (0.00%) 0	
Haemorrhage urinary tract subjects affected / exposed occurrences (all)	1 / 247 (0.40%) 1	0 / 122 (0.00%) 0	
Haematuria subjects affected / exposed occurrences (all)	1 / 247 (0.40%) 1	0 / 122 (0.00%) 0	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	2 / 247 (0.81%) 2	1 / 122 (0.82%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2010	Protocol version 2.0 has been submitted to Bulgaria (approval date: 28-Jul-2011), Czech Republic (approval date: 02-Aug-2011), Romania (not approved) and Germany (not approved).  Initial submission of regulatory package according to local requirements
21 October 2011	Protocol version 3.0 has been submitted to Bulgaria (approval date: 15-Mar-2012), Czech Republic (approval date: 27-Jan-2012), Romania (approval date: 03-Sep-2012), Austria (approval date: 16-Mar-2012), United Kingdom (not approved) and Germany (not approved).  Non-responders as identified based on the IEF at study end (Visit 4, Day 365 $\pm$ 14) will be offered a cell therapy in the scope of a subsequent, separate open-label study.
20 March 2012	Protocol version 4.0 has been submitted to Bulgaria (approval date: 03-Oct-2014), Czech Republic (approval date: 18-Nov-2014), Romania (approval date: 11-Dec-2014), Austria (approval date: 05-Aug-2014), United Kingdom (not approved) and Germany (18-Apr-2012).  Inclusion of 24 months follow-up: the follow-up phase consisted of three additional clinical visits: (start visit (SV), V5 (after 18 months of implantation) and visit 6 (after 24 months of implantation).

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported