# 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 |

**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 UKin 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 |
| **Arm title** | 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.

| | |
|---|---|
| **Arm title** | SMDC |

Arm description:

cell therapy 0.2 x 10e6 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 106 cells / 2 mL SMDCs injected into the external urethral sphincter

| **Number of subjects in period 1[1]** | Placebo | SMDC |
|---|---|---|
| Started | 125 | 252 |
| Completed | 113 | 235 |
| Not completed | 12 | 17 |
| Consent withdrawn by subject | 12 | 17 |

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 [1] |
| 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 |
|---|---|

End point description:

| 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[2] | 243[3] | | |
| 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 [4] |
| 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | SMDC |

Reporting group description: -

| | |
|---|---|
| Reporting group title | Placebo |

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 247 (0.40%) | 0 / 122 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 247 (0.40%) | 0 / 122 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haemorrhage urinary tract | | | |
| subjects affected / exposed | 1 / 247 (0.40%) | 0 / 122 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 247 (0.40%) | 0 / 122 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 247 (0.81%) | 1 / 122 (0.82%) | |
| occurrences (all) | 2 | 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).<br><br>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).<br><br>Non-responders as identified based on the IEF at study end (Visit 4, Day 365 ± 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).<br><br>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:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported