



## Clinical trial results:

### Skeletal muscle-derived cell implantation in female patients with stress urinary incontinence: a multinational and multicenter open follow-up study

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-001656-34 |
| Trial protocol           | BG             |
| Global end of trial date | 02 April 2015  |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 29 September 2021 |
| First version publication date | 29 September 2021 |

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | IC-01-01-05-015 |
|-----------------------|-----------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |                                                            |
|------------------------------|------------------------------------------------------------|
| Sponsor organisation name    | Innovacell AG                                              |
| Sponsor organisation address | Mitterweg 24, Innsbruck, Austria, 6020                     |
| Public contact               | Clinical Development, Innovacell AG, office@innovacell.com |
| Scientific contact           | Clinical Development, 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:

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**Results analysis stage**

|                                                      |               |
|------------------------------------------------------|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 06 June 2016  |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 02 March 2015 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 02 April 2015 |
| Was the trial ended prematurely?                     | No            |

Notes:

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**General information about the trial**

Main objective of the trial:

To show the long term efficacy and safety of the skeletal muscle-derived cell therapy

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                          | 18 August 2014 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Bulgaria: 42 |
| Worldwide total number of subjects   | 42           |
| EEA total number of subjects         | 42           |

Notes:

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**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)                      | 28 |
| From 65 to 84 years                       | 14 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

No treatment was administered within the study. Only patients were allowed to participate in the study who were part of the preceeding phase IIb study.

### Pre-assignment

Screening details:

Only patients from the previously performed phase IIb study who received cells and who were randomized to one of the two cell groups (0.2 x 10e6 [low cell count] aSMDC or 10 x 10e6 [high cell count] aSMDC).

### Period 1

|                              |                            |
|------------------------------|----------------------------|
| Period 1 title               | Follow-up (overall period) |
| Is this the baseline period? | Yes                        |
| Allocation method            | Randomised - controlled    |
| Blinding used                | Not blinded                |

### Arms

|                              |                |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes            |
| <b>Arm title</b>             | Low Cell Count |

Arm description:

0.2 x 10e6 autologous skeletal muscle-derived cells (aSMDCs) were administered with a standardized, ultrasound-directed, transurethral injection device under general anesthesia.

|                                        |                                          |
|----------------------------------------|------------------------------------------|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | Autologous skeletal muscle-derived cells |
| Investigational medicinal product code |                                          |
| Other name                             | ICES13                                   |
| Pharmaceutical forms                   | Suspension for injection                 |
| Routes of administration               | Injection , Intramuscular use            |

Dosage and administration details:

The IMP (0.2 ± 1 x 10e6 cells) is stored and transported as one vial, frozen in liquid nitrogen in 2 mL cell transportation medium. aSMDC were obtained from each patient by muscle biopsy. After in vitro purification and appropriate passages, the aSMDC were injected into the rhabdosphincter of the respective patient using a standardddized, ultrasoud-directed, transurethral injection tool. The administration of the aSMDC was performed under general anesthesia.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | High Cell Group |
|------------------|-----------------|

Arm description:

10 x 10e6 autologous skeletal muscle-derived cells (aSMDCs) were administered with a standardized, ultrasound-directed, transurethral injection device under general anesthesia.

|                                        |                                          |
|----------------------------------------|------------------------------------------|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | Autologous skeletal muscle-derived cells |
| Investigational medicinal product code |                                          |
| Other name                             | ICES13                                   |
| Pharmaceutical forms                   | Suspension for injection                 |
| Routes of administration               | Injection , Intramuscular use            |

Dosage and administration details:

The IMP (10 x 10e6 cells) is stored and transported as one vial, frozen in liquid nitrogen in 2 mL cell transportation medium. aSMDC were obtained from each patient by muscle biopsy. After in vitro purification and appropriate passages, the aSMDC were injected into the rhabdosphincter of the respective patient using a standardddized, ultrasoud-directed, transurethral injection tool. The administration of the aSMDC was performed under general anesthesia.

| <b>Number of subjects in period 1</b> | Low Cell Count | High Cell Group |
|---------------------------------------|----------------|-----------------|
| Started                               | 23             | 19              |
| Completed                             | 23             | 19              |

## Baseline characteristics

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Low Cell Count |
|-----------------------|----------------|

Reporting group description:

0.2 x 10e6 autologous skeletal muscle-derived cells (aSMDCs) were administered with a standardized, ultrasound-directed, transurethral injection device under general anesthesia.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | High Cell Group |
|-----------------------|-----------------|

Reporting group description:

10 x 10e6 autologous skeletal muscle-derived cells (aSMDCs) were administered with a standardized, ultrasound-directed, transurethral injection device under general anesthesia.

| Reporting group values                             | Low Cell Count | High Cell Group | Total |
|----------------------------------------------------|----------------|-----------------|-------|
| Number of subjects                                 | 23             | 19              | 42    |
| 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                                    | 60.96          | 55.56           |       |
| standard deviation                                 | ± 12.6         | ± 10.75         | -     |
| Gender categorical                                 |                |                 |       |
| Units: Subjects                                    |                |                 |       |
| Female                                             | 23             | 19              | 42    |
| Male                                               | 0              | 0               | 0     |

## End points

### End points reporting groups

|                                                                                                                                                                                                                   |                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Reporting group title                                                                                                                                                                                             | Low Cell Count  |
| Reporting group description:<br>0.2 x 10e6 autologous skeletal muscle-derived cells (aSMDCs) were administered with a standardized, ultrasound-directed, transurethral injection device under general anesthesia. |                 |
| Reporting group title                                                                                                                                                                                             | High Cell Group |
| Reporting group description:<br>10 x 10e6 autologous skeletal muscle-derived cells (aSMDCs) were administered with a standardized, ultrasound-directed, transurethral injection device under general anesthesia.  |                 |

### Primary: Incontinence Episode Frequency

|                                                                                                                                                                                |                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| End point title                                                                                                                                                                | Incontinence Episode Frequency |
| End point description:<br>Change in the Incontinence Episode Frequency (IEF) score compared to pre-treatment baseline measured in predecessor phase II study (2009-011797-15). |                                |
| End point type                                                                                                                                                                 | Primary                        |
| End point timeframe:<br>48 months post treatment                                                                                                                               |                                |

| End point values                     | Low Cell Count        | High Cell Group       |  |  |
|--------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                   | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed          | 23                    | 19                    |  |  |
| Units: IEF change                    |                       |                       |  |  |
| arithmetic mean (standard deviation) | -19.21 ( $\pm$ 11.89) | -13.95 ( $\pm$ 10.78) |  |  |

### Statistical analyses

|                                         |                                       |
|-----------------------------------------|---------------------------------------|
| Statistical analysis title              | High cell group versus Low cell group |
| Comparison groups                       | Low Cell Count v High Cell Group      |
| Number of subjects included in analysis | 42                                    |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | equivalence                           |
| P-value                                 | > 0.05 <sup>[1]</sup>                 |
| Method                                  | t-test, 1-sided                       |

Notes:

[1] - A p-value of <0.05 refers to statistical difference

### Secondary: VAS scale assessment

|                 |                      |
|-----------------|----------------------|
| End point title | VAS scale assessment |
|-----------------|----------------------|

End point description:

The individual perception of SUI complaints was evaluated by each patient using a standardized VAS; an instrument that measures a characteristic or attitude believed to range across a continuum of values and cannot be easily measured directly. The VAS used was a line of 100 mm in length, anchored by word descriptors at each end. Two endpoints were defined on the VAS: "no complaint at all" (0 mm) and "worst complaints imaginable" (100 mm).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 months post implantation

| End point values                     | Low Cell Count  | High Cell Group |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 23              | 19              |  |  |
| Units: mm                            |                 |                 |  |  |
| arithmetic mean (standard deviation) | 15.5 (± 17.55)  | 23.08 (± 26.65) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Responder Rate 25%

|                 |                    |
|-----------------|--------------------|
| End point title | Responder Rate 25% |
|-----------------|--------------------|

End point description:

Responders were defined as patients with a decrease in the IEF score by 25% at V2 (48M) compared to baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 months post implantation

| End point values            | Low Cell Count  | High Cell Group |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 23              | 19              |  |  |
| Units: 25%                  | 3               | 3               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Responder Rate 50%

|                 |                    |
|-----------------|--------------------|
| End point title | Responder Rate 50% |
|-----------------|--------------------|

End point description:

Responders were defined as patients with a decrease in the IEF score by 50% at V2 (48M) compared to baseline

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 months post implantation

| End point values            | Low Cell Count  | High Cell Group |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 23              | 19              |  |  |
| Units: number of patients   | 4               | 1               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Responder Rate 75%

|                 |                    |
|-----------------|--------------------|
| End point title | Responder Rate 75% |
|-----------------|--------------------|

End point description:

Responders were defined as patients with a decrease in the IEF score by 75% at V2 (48M) compared to baseline

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 months post implantation

| End point values            | Low Cell Count  | High Cell Group |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 23              | 19              |  |  |
| Units: number of patients   | 5               | 4               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Responder rate 90%

|                 |                    |
|-----------------|--------------------|
| End point title | Responder rate 90% |
|-----------------|--------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|



End point timeframe:

Responders were defined as patients with a decrease in the IEF score by 90% at V2 (48M) compared to baseline

| End point values            | Low Cell Count  | High Cell Group |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 23              | 19              |  |  |
| Units: number of patients   | 9               | 8               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: I-QoL (Scale Score total)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | I-QoL (Scale Score total) |
| End point description:<br>patients' health-related quality of life was assessed using the urinary I-QoL score, a self-administered quality of life instrument specific to persons with stress- and mixed types of UI. It includes general questions on eliciting all areas of concern and specific probes into hypothesized areas of impact: social life, family life, job/work, intimate relationships, activities of daily life, household activities, recreation and travel, mental health, physical health, and anxiety/depression. I-QoL includes 22 items divided into three domains: Avoidance and Limiting Behavior (ALB), Psychosocial Impacts (PSI), and Social Embarrassment (SE). Each item scores on a 5-point Likert scale comprising the categories "extremely", "quite a bit", "moderately", "a little", and "none at all". The best health state is assessed with a score of 5, standing for "none at all", and the worst health state has a score of 1 standing for "extremely". Higher scores indicate better health related quality of life. |                           |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Secondary                 |
| End point timeframe:<br>Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                           |

| End point values                     | Low Cell Count  | High Cell Group |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 23              | 19              |  |  |
| Units: Total Score                   |                 |                 |  |  |
| arithmetic mean (standard deviation) | 35.27 (± 21.09) | 45.23 (± 24.54) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: I-QoL (Scale Score total)

|                 |                           |
|-----------------|---------------------------|
| End point title | I-QoL (Scale Score total) |
|-----------------|---------------------------|

**End point description:**

Patients' health-related quality of life was assessed using the urinary I-QoL score, a self-administered quality of life instrument specific to persons with stress- and mixed types of UI. It includes general questions on eliciting all areas of concern and specific probes into hypothesized areas of impact: social life, family life, job/work, intimate relationships, activities of daily life, household activities, recreation and travel, mental health, physical health, and anxiety/depression. I-QoL includes 22 items divided into three domains: Avoidance and Limiting Behavior (ALB), Psychosocial Impacts (PSI), and Social Embarrassment (SE). Each item scores on a 5-point Likert scale comprising the categories "extremely", "quite a bit", "moderately", "a little", and "none at all". The best health state is assessed with a score of 5, standing for "none at all", and the worst health state has a score of 1 standing for "extremely". Higher scores indicate better health related quality of life.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 months post implantation

| End point values                     | Low Cell Count      | High Cell Group      |  |  |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group      |  |  |
| Number of subjects analysed          | 23                  | 19                   |  |  |
| Units: Total Score                   |                     |                      |  |  |
| arithmetic mean (standard deviation) | 82.78 ( $\pm$ 18.7) | 83.84 ( $\pm$ 18.45) |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Clinical Global impression (CGI) score**

|                 |                                        |
|-----------------|----------------------------------------|
| End point title | Clinical Global impression (CGI) score |
|-----------------|----------------------------------------|

End point description:

The CGI scale is a standardized assessment tool which allows physicians to rate severity of illness, changes over time and treatment efficiency, taking into account patients' clinical condition and the severity of side effects (1, normal, not at all ill, 2, borderline ill, 3, mildly ill, 4, moderately ill, 5, markedly ill, 6, severely ill, 7, among the most extremely ill patients).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline

| End point values                     | Low Cell Count     | High Cell Group  |  |  |
|--------------------------------------|--------------------|------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group  |  |  |
| Number of subjects analysed          | 23                 | 19               |  |  |
| Units: CGI score                     |                    |                  |  |  |
| arithmetic mean (standard deviation) | 3.53 ( $\pm$ 0.75) | 3.7 ( $\pm$ 0.8) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical Global Impression (CGI)

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Clinical Global Impression (CGI) |
|-----------------|----------------------------------|

End point description:

The CGI scale is a standardized assessment tool which allows physicians to rate severity of illness, changes over time and treatment efficiency, taking into account patients' clinical condition and the severity of side effects (1, normal, not at all ill, 2, borderline ill, 3, mildly ill, 4, moderately ill, 5, markedly ill, 6, severely ill, 7, among the most extremely ill patients).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 months post implantation

| End point values                     | Low Cell Count     | High Cell Group    |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 23                 | 19                 |  |  |
| Units: CGI Score                     |                    |                    |  |  |
| arithmetic mean (standard deviation) | 2.57 ( $\pm$ 1.21) | 2.84 ( $\pm$ 1.42) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Patient Global Impression - Improvement (PGI-I)

|                 |                                                 |
|-----------------|-------------------------------------------------|
| End point title | Patient Global Impression - Improvement (PGI-I) |
|-----------------|-------------------------------------------------|

End point description:

The Patient Global Impression of improvement (PGI-I) score is the patient reported outcomes counterpart to the CGI and was published in 1976 by the National Institute of Mental Health (US). This scale evaluates all aspects of patients' health and assesses if there has been an improvement or decline in clinical status (1, very much better, 2, much better, 3, a little better, 4, no change, 5, a little worse, 6, much worse, 7, very much worse)

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

48 months post implantation

| End point values                     | Low Cell Count     | High Cell Group    |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 23                 | 19                 |  |  |
| Units: PGI-I score                   |                    |                    |  |  |
| arithmetic mean (standard deviation) | 2.52 ( $\pm$ 1.21) | 2.53 ( $\pm$ 1.35) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: VAS scale assessment

|                 |                      |
|-----------------|----------------------|
| End point title | VAS scale assessment |
|-----------------|----------------------|

End point description:

The individual perception of SUI complaints was evaluated by each patient using a standardized VAS; an instrument that measures a characteristic or attitude believed to range across a continuum of values and cannot be easily measured directly. The VAS used was a line of 100 mm in length, anchored by word descriptors at each end. Two endpoints were defined on the VAS: "no complaint at all" (0 mm) and "worst complaints imaginable" (100 mm).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline

| End point values                     | Low Cell Count  | High Cell Group |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 23              | 19              |  |  |
| Units: mm                            |                 |                 |  |  |
| arithmetic mean (standard deviation) | 36.65 (± 16.9)  | 30.37 (± 17.17) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

Adverse events reporting was performed from September 2014 to April 2015.

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Adverse event reporting additional description:

This was a follow-up study without any treatment administered.

No adverse events were observed, thus no analysis, reporting and follow-up regarding adverse events was required.

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|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

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### Dictionary used

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|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

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|                    |      |
|--------------------|------|
| Dictionary version | 12.0 |
|--------------------|------|

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

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Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No treatment was administered during this follow-up study.

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported