



## Clinical trial results:

### Prevention of bladder dysfunction in acute spinal cord injury

**A double-blind, randomized, placebo-controlled study to explore the effect of early treatment with Onabotulinumtoxin A in patients with detrusor overactivity due to spinal cord injury**

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-002211-25 |
| Trial protocol           | NO             |
| Global end of trial date | 12 March 2019  |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 08 September 2021 |
| First version publication date | 08 September 2021 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | bot001 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01698138 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Oslo University Hospital   |
| Sponsor organisation address | Sognsvannsveien 20, OSLO, Norway, 0372   |
| Public contact               | Dept of Urology, Reconstructive urology, Oslo University Hospital, 47 23070000, ole.jacob.nilsen@ous-hf.no |
| Scientific contact           | Dept of Urology, Reconstructive urology, Oslo University Hospital, 47 23070000, ole.jacob.nilsen@ous-hf.no |

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                       | 12 March 2019 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 12 March 2019 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 12 March 2019 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To investigate if intravesical injection of Botox can prevent the development of bladder dysfunction after spinal cord injury

Protection of trial subjects:

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

The study subjects will be recruited shortly after a serious injury. Timing of information is very difficult in this category of patients, and must take into account the subject's ability to process and cope with all the possible complications of their injury. Even though the prognosis is usually known two weeks post injury, many patients and relatives have still not been informed about all aspects of the injury. Obtaining informed consent without adequate information is unethical. However, giving information too early may provoke depression and other psychological reactions. Consequently, we will approach the study subject with care, and only provide detailed information about the study if we consider the subjects to be able to cope with the information. Studies have previously been conducted in this group of patients (6).

The study will involve intradetrusor injections of Onabotulinumtoxin A and bladder biopsies.

Intradetrusor injection of Onabotulinumtoxin A is an established treatment for NDO, with a low rate of complications and adverse events (15). Known complications to bladder biopsies are bleeding and perforation of the bladder. To avoid the risk of intraperitoneal bladder perforations, bladder biopsies will be taken from the bladder base. An experienced consultant urologist will perform the procedures. The participants will be treated as in-patients during the procedures and follow-up. These patients are routinely given anticoagulant therapy. To avoid excessive haematuria, anticoagulant therapy will be discontinued in connection with the procedures. This may increase the risk of thromboembolism.

Background therapy: -

Evidence for comparator: -

|   |                               |
|---|-------------------------------|
| Actual start date of recruitment                          | 01 August 2012                |
| Long term follow-up planned                               | Yes                           |
| Long term follow-up rationale                             | Scientific research, Efficacy |
| Long term follow-up duration                              | 10 Years                      |
| Independent data monitoring committee (IDMC) involvement? | No                            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Norway: 9 |
| Worldwide total number of subjects   | 9         |
| EEA total number of subjects         | 9         |

Notes:

| <b>Subjects enrolled per age group</b>    |   |
|---|---|
| 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)                      | 9 |
| From 65 to 84 years                       | 0 |
| 85 years and over                         | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Patients with acute spinal cord injury (above Th11) will be included within twelve weeks from the time of injury. Before randomization, the patients will be investigated with video urodynamics to make sure the bladder is atonic and in spinal shock. Patients who have developed NDO will be excluded.

### Period 1

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

### Arms

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

Arm description:

Placebo injection

|  |                                    |
|--|------------------------------------|
| Arm type                               | Placebo                            |
| Investigational medicinal product name | NaCl 0,9%                          |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Solution for solution for infusion |
| Routes of administration               | Solution for infusion              |

Dosage and administration details:

intradetrusor injection of 30 ml of NaCl 0.9 %

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Onabotulinumtoxin A |
|------------------|---------------------|

Arm description: -

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Onabotulinumtoxin A |
| Investigational medicinal product code |                     |
| Other name                             | Botox               |
| Pharmaceutical forms                   | Infusion            |
| Routes of administration               | Infusion            |

Dosage and administration details:

intradetrusor injection of 300 U Onabotulinumtoxin A (Botox®, «Allergan») in 30 ml of NaCl 0.9 %

| <b>Number of subjects in period 1</b> | Placebo | Onabotulinumtoxin A |
|---------------------------------------|---------|---------------------|
| Started                               | 4       | 5                   |
| Completed                             | 4       | 5                   |



## Baseline characteristics

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### Reporting groups

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

Reporting group description:

Placebo injection

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Onabotulinumtoxin A |
|-----------------------|---------------------|

Reporting group description: -

| Reporting group values | Placebo | Onabotulinumtoxin A | Total |
|------------------------|---------|---------------------|-------|
| Number of subjects     | 4       | 5                   | 9     |
| Age categorical        |         |                     |       |
| Units: Subjects        |         |                     |       |
| Adults (18-64 years)   | 4       | 5                   | 9     |
| Gender categorical     |         |                     |       |
| Units: Subjects        |         |                     |       |
| Female                 | 0       | 0                   | 0     |
| Male                   | 4       | 5                   | 9     |

## End points

### End points reporting groups

|   |                     |
|---|---------------------|
| Reporting group title                             | Placebo             |
| Reporting group description:<br>Placebo injection |                     |
| Reporting group title                             | Onabotulinumtoxin A |
| Reporting group description: -                    |                     |

### Primary: Presence of neurogenic detrusor overactivity during cystometry

|                                   |  |
|-----------------------------------|--|
| End point title                   | Presence of neurogenic detrusor overactivity during cystometry |
| End point description:            |  |
| End point type                    | Primary  |
| End point timeframe:<br>12 months |  |

| End point values                         | Placebo         | Onabotulinumtoxin A |  |  |
|--|-----------------|---------------------|--|--|
| Subject group type                       | Reporting group | Reporting group     |  |  |
| Number of subjects analysed              | 4               | 5                   |  |  |
| Units: Contracts                         |                 |                     |  |  |
| Contraction with amplitude over 40cm H2O | 2               | 0                   |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | suissa-shuster exact unconditional test |
| Comparison groups                       | Placebo v Onabotulinumtoxin A           |
| Number of subjects included in analysis | 9                                       |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.11                                  |
| Method                                  | suissa-shuster exact unconditional test |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The standard time period for collecting and recording AE and SAEs will begin at administration of first dose of study drug, up til 12 months follow up.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 24     |

### Reporting groups

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

Reporting group description: -

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Botox-treated group |
|-----------------------|---------------------|

Reporting group description: -

| Serious adverse events                            | Placebo Group  | Botox-treated group |  |
|---|----------------|---------------------|--|
| Total subjects affected by serious adverse events |                |                     |  |
| subjects affected / exposed                       | 1 / 4 (25.00%) | 2 / 5 (40.00%)      |  |
| number of deaths (all causes)                     | 0              | 0                   |  |
| number of deaths resulting from adverse events    | 0              |                     |  |
| Respiratory, thoracic and mediastinal disorders   |                |                     |  |
| Pulmonary embolism                                |                |                     |  |
| alternative assessment type: Non-systematic       |                |                     |  |
| subjects affected / exposed                       | 0 / 4 (0.00%)  | 1 / 5 (20.00%)      |  |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1               |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0               |  |
| Renal and urinary disorders                       |                |                     |  |
| Urinary tract infection bacterial                 |                |                     |  |
| alternative assessment type: Non-systematic       |                |                     |  |
| subjects affected / exposed                       | 1 / 4 (25.00%) | 0 / 5 (0.00%)       |  |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0               |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0               |  |
| Musculoskeletal and connective tissue disorders   |                |                     |  |
| Muscle haemorrhage                                |                |                     |  |



|   |               |                |  |
|---|---------------|----------------|--|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 5 (20.00%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Placebo Group   | Botox-treated group |  |
|---|-----------------|---------------------|--|
| Total subjects affected by non-serious adverse events |                 |                     |  |
| subjects affected / exposed                           | 4 / 4 (100.00%) | 5 / 5 (100.00%)     |  |
| Injury, poisoning and procedural complications        |                 |                     |  |
| knee injury   |                 |                     |  |
| subjects affected / exposed                           | 1 / 4 (25.00%)  | 0 / 5 (0.00%)       |  |
| occurrences (all)                                     | 1               | 0                   |  |
| Back pain   |                 |                     |  |
| subjects affected / exposed                           | 1 / 4 (25.00%)  | 0 / 5 (0.00%)       |  |
| occurrences (all)                                     | 1               | 0                   |  |
| Vascular disorders                                    |                 |                     |  |
| Deep vein thrombosis                                  |                 |                     |  |
| subjects affected / exposed                           | 0 / 4 (0.00%)   | 1 / 5 (20.00%)      |  |
| occurrences (all)                                     | 0               | 1                   |  |
| Blood and lymphatic system disorders                  |                 |                     |  |
| Haematoma   |                 |                     |  |
| subjects affected / exposed                           | 1 / 4 (25.00%)  | 0 / 5 (0.00%)       |  |
| occurrences (all)                                     | 1               | 0                   |  |
| Skin and subcutaneous tissue disorders                |                 |                     |  |
| Dermatitis  |                 |                     |  |
| subjects affected / exposed                           | 1 / 4 (25.00%)  | 0 / 5 (0.00%)       |  |
| occurrences (all)                                     | 2               | 0                   |  |
| Renal and urinary disorders                           |                 |                     |  |
| Urinary tract infection bacterial                     |                 |                     |  |
| subjects affected / exposed                           | 4 / 4 (100.00%) | 5 / 5 (100.00%)     |  |
| occurrences (all)                                     | 15              | 16                  |  |
| Infections and infestations                           |                 |                     |  |
| Conjunctivitis  |                 |                     |  |
| subjects affected / exposed                           | 0 / 4 (0.00%)   | 1 / 5 (20.00%)      |  |
| occurrences (all)                                     | 0               | 1                   |  |



## **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