



## Clinical trial results:

### The reversed isolated forearm technique to regionally reverse rocuronium induced muscle relaxation – a pilot study

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2013-002164-53    |
| Trial protocol           | AT                |
| Global end of trial date | 24 September 2015 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 27 March 2020 |
| First version publication date | 27 March 2020 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 20130513 |
|-----------------------|----------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |                                                                                                                                                                       |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Medical University of Vienna                                                                                                                                          |
| Sponsor organisation address | Spitalgasse 23, Vienna, Austria,                                                                                                                                      |
| Public contact               | Forschungsbüro, Fr. Mag. Vecs, Medizinische Universität Wien, Abteilung für Allgemeine Anästhesie und Intensivmedizin, +43 1404002031, eleonora.vecs@meduniwien.ac.at |
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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                       | 25 September 2015 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 24 September 2015 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 24 September 2015 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the feasibility of regionally reversing a rocuronium induced muscle relaxation and to determine the dose of sugammadex that is necessary to reach a train of four (TOF) ratio  $\geq 0.9$ .

Protection of trial subjects:

Patients were closely observed intra- and postoperatively for any adverse reaction to the intervention.

Background therapy:

Elective surgery with the need of general anaesthesia and muscle relaxation with rocuronium.

Evidence for comparator:

No comparator

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 09 December 2013 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Austria: 20 |
| Worldwide total number of subjects   | 20          |
| EEA total number of subjects         | 20          |

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)                      | 20 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Patients undergoing an elective operation with the need of general anaesthesia with muscle relaxation were asked preoperatively if they want to participate in the study.

### Pre-assignment

Screening details:

Patients undergoing an elective operation with the need of general anaesthesia with muscle relaxation were screened for eligibility preoperatively

### Period 1

|                              |                |
|------------------------------|----------------|
| Period 1 title               | Baseline       |
| Is this the baseline period? | Yes            |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

Blinding implementation details:

none

### Arms

|           |          |
|-----------|----------|
| Arm title | Baseline |
|-----------|----------|

Arm description:

Patients before proceeding to period "Dose finding" or "Dose effect"

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | no intervention |
| Investigational medicinal product name | none            |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Other use       |

Dosage and administration details:

no product was used at baseline

|                                       |          |
|---------------------------------------|----------|
| <b>Number of subjects in period 1</b> | Baseline |
| Started                               | 20       |
| Completed                             | 20       |

### Period 2

|                              |                |
|------------------------------|----------------|
| Period 2 title               | Dose finding   |
| Is this the baseline period? | No             |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

Blinding implementation details:

none

## Arms

| Arm title | Dose finding |
|-----------|--------------|
|-----------|--------------|

Arm description:

The dose-titration process was designed as follows. The initial dose in the first patient was set to be sugammadex 0.5 mg kg<sup>-1</sup> diluted in 30 ml normal saline. If the TOF ratio remained below 0.9 for the next 5 min, a top-up dose of one-quarter of this dose (e.g. sugammadex 0.125 mg kg<sup>-1</sup> in Patient 1) diluted in 10 ml of 0.9% saline was administered. This procedure was repeated until a stable TOF ratio  $\geq 0.9$  (three consecutive measurements  $\geq 0.9$ ) was reached in the interventional limb or until a total of four injections were given. If a TOF ratio  $\geq 0.9$  was achieved with this titration, the initial and top-up sugammadex doses in the next patient were reduced to one-quarter of the initial dose given to the previous patient but were still diluted in 30 ml saline (10 ml for top-up doses). For example, if the muscle paralysis of Patient 1 was antagonized after the initial dose of sugammadex 0.5 mg kg<sup>-1</sup>, the initial and the top-up doses would be reduced to 1.25 mg kg<sup>-1</sup> in Patient 2.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Sugammadex      |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intravenous use |

Dosage and administration details:

The dose-titration process was designed as follows. The initial dose in the first patient was set to be sugammadex 0.5 mg kg<sup>-1</sup> diluted in 30 ml normal saline. If the TOF ratio remained below 0.9 for the next 5 min, a top-up dose of one-quarter of this dose (e.g. sugammadex 0.125 mg kg<sup>-1</sup> in Patient 1) diluted in 10 ml of 0.9% saline was administered. This procedure was repeated until a stable TOF ratio  $\geq 0.9$  (three consecutive measurements  $\geq 0.9$ ) was reached in the interventional limb or until a total of four injections were given. If a TOF ratio  $\geq 0.9$  was achieved with this titration, the initial and top-up sugammadex doses in the next patient were reduced to one-quarter of the initial dose given to the previous patient but were still diluted in 30 ml saline (10 ml for top-up doses). For example, if the muscle paralysis of Patient 1 was antagonized after the initial dose of sugammadex 0.5 mg kg<sup>-1</sup>, the initial and the top-up doses would be reduced to 1.25 mg kg<sup>-1</sup> in Patient 2.

| Number of subjects in period 2 <sup>[1]</sup> | Dose finding |
|-----------------------------------------------|--------------|
| Started                                       | 10           |
| Completed                                     | 10           |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 20 Patients were included at baseline, 10 of these patients participated in study period "dose finding" and 10 of the patients participated in the period "time to effect". All patients completed the study

## Period 3

|                              |                |
|------------------------------|----------------|
| Period 3 title               | Dose effect    |
| Is this the baseline period? | No             |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

Blinding implementation details:

none

## Arms

| Arm title | Dose Effect |
|-----------|-------------|
|-----------|-------------|

### Arm description:

In this group, dose titration was not performed, and all patients received the same amount of sugammadex diluted in the same volume (30 ml normal saline). The TOF was again measured every 15 s in both arms, and the effects of the sugammadex dose on muscle paralysis in both arms were recorded. The tourniquet was released 15 min after sugammadex was injected, and the effect of this dose on the TOF values in both arms was recorded until the TOF ratio returned to  $\geq 0.9$  in both arms.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Sugammadex      |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intravenous use |

### Dosage and administration details:

In this group, dose titration was not performed, and all patients received the same amount of sugammadex diluted in the same volume (30 ml normal saline). The TOF was again measured every 15 s in both arms, and the effects of the sugammadex dose on muscle paralysis in both arms were recorded. The tourniquet was released 15 min after sugammadex was injected, and the effect of this dose on the TOF values in both arms was recorded until the TOF ratio returned to  $\geq 0.9$  in both arms.

| Number of subjects in period 3 | Dose Effect |
|--------------------------------|-------------|
| Started                        | 10          |
| Completed                      | 10          |

## Baseline characteristics

### Reporting groups

|                                |          |
|--------------------------------|----------|
| Reporting group title          | Baseline |
| Reporting group description: - |          |

| Reporting group values   | Baseline | Total |  |
|--------------------------|----------|-------|--|
| Number of subjects       | 20       | 20    |  |
| Age categorical          |          |       |  |
| Baseline characteristics |          |       |  |
| Units: Subjects          |          |       |  |
| Adults (18-64 years)     | 20       | 20    |  |
| Age continuous           |          |       |  |
| Units: years             |          |       |  |
| arithmetic mean          | 38       |       |  |
| standard deviation       | ± 12     | -     |  |
| Gender categorical       |          |       |  |
| Units: Subjects          |          |       |  |
| Female                   | 10       | 10    |  |
| Male                     | 10       | 10    |  |

### Subject analysis sets

|                            |                            |
|----------------------------|----------------------------|
| Subject analysis set title | Dose finding of sugammadex |
| Subject analysis set type  | Per protocol               |

Subject analysis set description:  
descriptive

|                            |                |
|----------------------------|----------------|
| Subject analysis set title | Dose to effect |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:  
descriptive

| Reporting group values   | Dose finding of sugammadex | Dose to effect |  |
|--------------------------|----------------------------|----------------|--|
| Number of subjects       | 10                         | 10             |  |
| Age categorical          |                            |                |  |
| Baseline characteristics |                            |                |  |
| Units: Subjects          |                            |                |  |
| Adults (18-64 years)     | 10                         | 10             |  |
| Age continuous           |                            |                |  |
| Units: years             |                            |                |  |
| arithmetic mean          | 50                         | 40             |  |
| standard deviation       | ± 11                       | ± 14           |  |
| Gender categorical       |                            |                |  |
| Units: Subjects          |                            |                |  |
| Female                   | 5                          | 5              |  |
| Male                     | 5                          | 5              |  |

## End points

### End points reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Baseline |
|-----------------------|----------|

Reporting group description:

Patients before proceeding to period "Dose finding" or "Dose effect"

|                       |              |
|-----------------------|--------------|
| Reporting group title | Dose finding |
|-----------------------|--------------|

Reporting group description:

The dose-titration process was designed as follows. The initial dose in the first patient was set to be sugammadex 0.5 mg kg<sup>-1</sup> diluted in 30 ml normal saline. If the TOF ratio remained below 0.9 for the next 5 min, a top-up dose of one-quarter of this dose (e.g. sugammadex 0.125 mg kg<sup>-1</sup> in Patient 1) diluted in 10 ml of 0.9% saline was administered. This procedure was repeated until a stable TOF ratio  $\geq 0.9$  (three consecutive measurements  $\geq 0.9$ ) was reached in the interventional limb or until a total of four injections were given. If a TOF ratio  $\geq 0.9$  was achieved with this titration, the initial and top-up sugammadex doses in the next patient were reduced to one-quarter of the initial dose given to the previous patient but were still diluted in 30 ml saline (10 ml for top-up doses). For example, if the muscle paralysis of Patient 1 was antagonized after the initial dose of sugammadex 0.5 mg kg<sup>-1</sup>, the initial and the top-up doses would be reduced to 1.25 mg kg<sup>-1</sup> in Patient 2.

|                       |             |
|-----------------------|-------------|
| Reporting group title | Dose Effect |
|-----------------------|-------------|

Reporting group description:

In this group, dose titration was not performed, and all patients received the same amount of sugammadex diluted in the same volume (30 ml normal saline). The TOF was again measured every 15 s in both arms, and the effects of the sugammadex dose on muscle paralysis in both arms were recorded. The tourniquet was released 15 min after sugammadex was injected, and the effect of this dose on the TOF values in both arms was recorded until the TOF ratio returned to  $\geq 0.9$  in both arms.

|                            |                            |
|----------------------------|----------------------------|
| Subject analysis set title | Dose finding of sugammadex |
|----------------------------|----------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

descriptive

|                            |                |
|----------------------------|----------------|
| Subject analysis set title | Dose to effect |
|----------------------------|----------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

descriptive

### Primary: Dose of sugammadex

|                 |                    |
|-----------------|--------------------|
| End point title | Dose of sugammadex |
|-----------------|--------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

5 minutes after the application of sugammadex

| End point values            | Dose finding       | Dose finding of sugammadex |  |  |
|-----------------------------|--------------------|----------------------------|--|--|
| Subject group type          | Reporting group    | Subject analysis set       |  |  |
| Number of subjects analysed | 10                 | 10                         |  |  |
| Units: mg/kg                |                    |                            |  |  |
| median (standard deviation) | 0.02 ( $\pm$ 0.15) | 0.02 ( $\pm$ 0.15)         |  |  |

## Statistical analyses

|                                         |                                           |
|-----------------------------------------|-------------------------------------------|
| <b>Statistical analysis title</b>       | descriptive                               |
| Statistical analysis description:       |                                           |
| Descriptive analysis                    |                                           |
| Comparison groups                       | Dose finding v Dose finding of sugammadex |
| Number of subjects included in analysis | 20                                        |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | other <sup>[1]</sup>                      |
| P-value                                 | = 0.05 <sup>[2]</sup>                     |
| Method                                  | descriptive statistics                    |
| Parameter estimate                      | descriptive statistics                    |
| Notes:                                  |                                           |
| [1] - descriptive statistics            |                                           |
| [2] - not applicable                    |                                           |

## Primary: Time to reversal of rocuronium

|                                                     |                                |
|-----------------------------------------------------|--------------------------------|
| End point title                                     | Time to reversal of rocuronium |
| End point description:                              |                                |
|                                                     |                                |
| End point type                                      | Primary                        |
| End point timeframe:                                |                                |
| Time from the application of sugammadex to TOF >0.9 |                                |

|                                      |                 |                      |  |  |
|--------------------------------------|-----------------|----------------------|--|--|
| <b>End point values</b>              | Dose Effect     | Dose to effect       |  |  |
| Subject group type                   | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed          | 10              | 10                   |  |  |
| Units: minute                        |                 |                      |  |  |
| arithmetic mean (standard deviation) | 1.9 (± 1.3)     | 1.95 (± 1.35)        |  |  |

## Statistical analyses

|                                         |                              |
|-----------------------------------------|------------------------------|
| <b>Statistical analysis title</b>       | Time to effect               |
| Comparison groups                       | Dose Effect v Dose to effect |
| Number of subjects included in analysis | 20                           |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | other                        |
| P-value                                 | = 0.05 <sup>[3]</sup>        |
| Method                                  | descriptive statistics       |
| Parameter estimate                      | descriptive statistics       |
| Point estimate                          | 0                            |
| Confidence interval                     |                              |
| level                                   | Other: 0 %                   |
| sides                                   | 2-sided                      |
| lower limit                             | 0                            |
| upper limit                             | 0                            |



| Variability estimate | Standard deviation |
|----------------------|--------------------|
|----------------------|--------------------|

Notes:

[3] - not applicable

## Adverse events

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

Timeframe for reporting adverse events:  
at the day the study was performed

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 15 |
|--------------------|----|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | All patients |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events                            | All patients   |  |  |
|---------------------------------------------------|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 0 / 20 (0.00%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events                            | All patients   |  |  |
|-------------------------------------------------------|----------------|--|--|
| Total subjects affected by non-serious adverse events |                |  |  |
| subjects affected / exposed                           | 0 / 20 (0.00%) |  |  |

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: In this small feasibility study, no adverse event was observed.

## 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

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26934944>