## Clinical Study Protocol

# "Can adequacy of anesthesia depth and quality of recovery be influenced by the level of neuromuscular blockade: a randomized controlled study assessing propofol and remifentanil requirements and quality of recovery in patients with a standard practice of non-deep rocuronium neuromuscular blockade versus deep neuromuscular blockade reversed with sugammadex."

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Can adequacy of anesthesia depth and quality of recovery be influenced by the level of neuromuscular blockade?

# 1. General Information

## a) Title

Short title: Can adequacy of anesthesia depth and quality of recovery be influenced by the level of neuromuscular blockade?

Long title: Can adequacy of anesthesia depth and quality of recovery be influenced by the level of neuromuscular blockade: a randomized controlled study assessing propofol and remifentanil requirements and quality of recovery in patients with a standard practice of non-deep rocuronium neuromuscular blockade versus deep neuromuscular blockade reversed with sugammadex.

## b) Identification Code

Eudra CT # 2014-005238-76

Sponsor Protocol # 2014.145

## c) Version

Final 2.0

## d) Date

26th January 2016

## e) Investigator Agreement

"I have read this protocol and agree to conduct the trial according to the protocol and to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice, as well as applicable laws and regulations."

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### f) Sponsor representative

_____ _____

Sollari Allegro Date

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### h) Participating sites addresses

The following site will be involved in this study:

- Centro Hospitalar do Porto, EPE – Hospital de Santo António

### i) Supporting institutions

The following institutions will provide support to the study

- NOVA Clinical Research Unit (NOVA-CRU) of Chronic Diseases Research Center of NOVA Medical School (CEDOC-FCM-UNL):
    - Study Submission
    - Monitoring

## 2. Protocol synopsis

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|---|---|
| Title | Can adequacy of anesthesia depth and quality of recovery be influenced by the level of neuromuscular blockade: a randomized controlled study assessing propofol and remifentanil requirements and quality of recovery in patients with a standard practice of non-deep rocuronium neuromuscular blockade versus deep neuromuscular blockade reversed with sugammadex |
| Trial Code | Eudra CT # 2014-005238-76 |
| Trial Phase | IV |
| Trial Design | This will be an interventional, randomized, unblended, parallel-arm single-center study |
| Rationale | We hypothesise that an anesthetic protocol maintaining deep neuromuscular block throughout the entire surgical procedure followed by sugammadex reversal, would suppress EMG activity and result in improved anesthetic stability by reducing the variability of the Bispectral Index of the EEG, and be beneficial by reducing the total doses of the anesthetic drugs propofol and remifentanil required to maintain an adequate level of anesthesia (BIS between 40 and 60). |
| Participants | Patients with an ASA score of I to III, 18 to 80 years old, scheduled for routine anterior cervical spine surgery in the Centro Hospitalar do Porto will be enrolled. |
| Selection Criteria | Inclusion criteria<br>• Patients ASA I-III<br>• Between 18 – 80 years old<br>• scheduled for routine cervical surgery |

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| | • Minimum duration of surgery is 90 minutes and performed with total intravenous anaesthesia (TIVA) with the hypnotic propofol, the analgesic remifentanil and the neuromuscular relaxant rocuronium<br>• Patients that are able to and do provide a signed informed consent form<br><br>Exclusion criteria<br><br>• Patients with neuromuscular diseases and severe cardiac and respiratory pathologies<br>• or that have any contra indication for any of the drugs used<br>• or that are not able to complete the baseline PQRS test.<br>• Indication to perform tracheal intubation using fibroscopy<br>• Patients who are pregnant or nursing. |
| Sample Size | Seventy patients will be enrolled. |
| Duration | 1 year and 4 months divided as follows:<br><br>• 4 months (from the preparation of the forms for submission to acceptance of the National Ethics Committee, National Committee for Data Protection, and National Authority of Medicines and Health Products – the estimated time for response of the National Committees is 2 months)<br>• 8 months for patient enrolment and data collection (an average of 2 patients per week)<br>• 2 months for finishing the database and statistical analysis |

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| | • 2 months for the analysis of results and finalizing the Clinical Report Study |
| Primary Objective | The objective of this study is to assess if the use of deep neuromuscular blockade reversed with sugammadex, and the consequent suppression of the EMG activity, can improve the overall stability of an anesthetic procedure (guided using BIS monitoring) and allow a reduction in the amount of anesthetic drugs required for adequate anesthesia.<br><br>Patients subjected to anterior cervical spine surgery under general intravenous anesthesia will be randomized to receive one of two protocols regarding the neuromuscular blockade: our institution's standard practice of non-deep rocuronium blockade or deep neuromuscular blockade reversed with sugammadex |
| Secondary Objectives | As a secondary objective, we will study the quality of recovery using the PQRS scale to see if maintaining a deep NMB level during surgery has an impact on the patients' quality of recovery. |
| Primary Endpoint | Anesthetic stability, measured by the variability of the Bispectral Index of the EEG |
| Secondary Endpoint | Quality of recovery using the PQRS scale |
| Intervention | Deep neuromuscular blockade reversed with sugammadex. |

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## 3. Abbreviations

| | |
|---|---|
| AE | Adverse event |
| ALT | Alanine transaminase |
| AST | Aspartate aminotransferase |
| BIS | Bispectral Index |
| CEIC | Portuguese Central Ethics Committee "Comissão de Ética para a Investigação Clínica" |
| CIOMS | Council for International Organizations of Medical Sciences |
| CNPD | Portuguese Data Privacy Agency "Comissão Nacional de Protecção de Dados" |
| DSUR | Development Safety Update Report |
| ECI | Event of Clinical Interest |
| eCRF | Electronic Case Report Form |
| EMG | Electromyography |
| GCP | Good Clinical Practice |
| IB | Investigator's Brochure |
| ICH | International Conference of Harmonization |
| IMP | Investigational Medicinal Product |
| Infarmed | Portuguese Regulatory Authority "Instituto da Farmácia e do Medicamento" |
| MAP | Mean Arterial Pressure |
| NIMP | Non Investigational Medicinal Product |

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|---|---|
| NMB | Neuromuscular blocade |
| PQC | Product Quality Complaint |
| PQRS | Physician Quality Reporting System |
| PTC | Post Tetanic Count |
| SAE | Seriouse adverse event |
| SMP | Summary of Product Characteristics |
| SUSAR | Serious Unexpected Suspected Adverse Reaction |
| TCI | Targeted controlled infusion |
| TOF | Train-of-four |
| ULN | Upper Limit Normal |

## 4. Background and rationale

The Bispectral Index (BIS) of the electroencephalogram (EEG) uses a four-electrode sensor placed on the forehead and is widely used as a quantifiable measure of depth of sedation and depth of anesthesia (DOA) [1-3]. Currently all DOA monitors are EEG based and use indexes similar to the BIS. Scientific evidence for the benefits of BIS guided anesthesia are abundant [4]. Insufficient anesthesia may cause Intraoperative awareness, which may be prevented by maintaining BIS values between 40 and 60 [5-7]. Excessive anesthesia, namely BIS below 45 or 40, is being increasingly associated with increased mortality at one or more years following surgery [8,9], especially if combined with hypotension [10]. Therefore, guiding anesthesia aiming at maintaining BIS within the recommended range offers important advantages. According to a recent NICE report it is also cost effective [11].

However, the presence of spontaneous electromyography (EMG) interferes with the EEG, in particular with frontal EEG, and studies show that EMG activity affects the accuracy of BIS monitoring [12-16]. The EMG interference can give

misleading information about depth of anesthesia. Panousis et al. reported that BIS values between 70 and 80 occurred intermittently above an EMG activity of 35 dB [16]. This correlation between BIS and EMG was observed under adequate DOA and analgesia. One of the reasons for this is the range overlap between the frequencies generated by muscle activity and the frequencies originated from the EEG [16].

Vivien et al. showed that increased BIS values (due to EMG) could be solved by the administration of a muscle relaxant [14]. This work showed that the magnitude of the BIS decrease following neuromuscular blockade was significantly correlated to both BIS and EMG values before myorelaxation, showing that a BIS-induced oversedation can happen if there is no adequate level of muscle relaxation. This conclusion is also in accordance with the work of Bruhn et at. [12], which shows that EMG falsely elevates BIS values in anesthetized patients without neuromuscular block (NMB).

The use of NMB reduces EMG activity and can, therefore, reduce the EMG interference on the EEG and derived indexes. Consequently, the BIS may be altered not by the use of NMB but by the removal of the EMG interference. Inoue et al. [15] studied the effect of NMB on systemic and cerebral hemodynamics as well as on BIS and showed that the EMG was significantly reduced by the use of NMB, both in deep or moderate sedation, but that cerebral hemodynamics were not altered by NMB. They also found that BIS and systemic hemodynamic variables at moderate sedation resembled the values at deep sedation in the presence of NMB, but that such values were different in the absence of NMB [15]. Another finding was that NMB might enhance cardiovascular stability. Considered together, these studies suggest that if NMB is used in a way that the EMG interference is removed from the EEG, one can observe values of BIS that reflect only the depressant effect of hypnotics and opioid analgesics on the EEG, obtaining BIS values that are lower than those "contaminated" by EMG. This could lead to a reduction of the doses of other anesthetic drugs (hypnotics and analgesics), an attenuation of side effects from their overdosage and cost reduction.

NMB is necessary to perform tracheal intubation and to avoid movement and muscle responses during surgery. Also, deep blockade is sometimes required.

However, in the past, maintenance of deep NMB was restricted by the nonexistence of a fast reversal drug. Because of this limitation, moderate levels of NMB provided by bolus or continuous infusions are often used, namely in combination with modern and more efficient hypnotics and analgesics. The new drug sugammadex allows for a prompt reversal for the relaxants vecuronium and rocuronium [17]. Therefore, a deep level of NMB can be maintained during general anesthesia allowing better surgical conditions and be promptly reversed for a safe, fast and comfortable recovery.

A recent study from Dahaba et al. [18], compared BIS values before and after sugammadex or neostigmine NMB reversal in patients with and without EMG activity and showed that reversal of NMB increased BIS values because of the presence of EMG activity. This needs to be taken into account when relying on BIS monitoring for assessing unconsciousness and recovery: an increase in BIS after NMB reversal may not imply arousal from general anesthesia, but just the return of EMG activity and subsequent monitoring interference. The opposite is also very important, since the clinician can increase the administration of hypnotic or analgesic in response to a increased BIS, in a situation where the BIS may be high due to EMG interference; this may render patients prone to a worse outcome as a consequence of excessive anesthesia [8,9].

The objective of the proposed study is to assess if deep NMB followed by sugammadex reversal, and the consequent intra-operative suppression of the EMG, can improve the overall stability of an anesthetic procedure (using BIS monitoring) and result in a reduction in the requirements of anesthetics (hypnotic and analgesic). Another objective is to evaluate if quality of recovery, as assessed by the Post-operative Quality of Recovery Scale (PQRS)[19,20], can be improved by using deep NMB, more adequate doses of anesthetic drugs and sugammadex reversal.

The Post-operative Quality of Recovery Scale (PQRS) was developed by a group of anaesthesiologists, with the intention to produce an instrument for the assessment of both early and long-term recovery [19, 20]. This is the first available tool for evaluating multiple domains of recovery - physiologic, cognitive, and functional recovery [19,20]. PQRS was validated in different languages (English; German; French; Spanish and Chinese) including a total of 701 patients. The

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Portuguese version has been translated and is at this time already available from the PQRS authors. The PQRS has already been successfully used by our research group in a previous study.

We hypothesise that an anesthetic protocol maintaining deep neuromuscular block throughout the entire surgical procedure followed by sugammadex reversal, would suppress EMG activity and result in improved anesthetic stability by reducing the variability of the Bispectral Index of the EEG, and be beneficial by reducing the total doses of the anesthetic drugs propofol and remifentanil required to maintain an adequate level of anesthesia (BIS between 40 and 60). Average anesthetic requirements will be assessed by using the average effect-site concentrations of propofol and remifentanil, since they take into account the patient gender, weight and height and are, therefore, more representative of the drug requirements.

As secondary hypothesis we also expect to observe an increase in the quality of recovery (assessed by the Postoperative Quality of Recovery Scale – PQRS) and a decrease in the amount of ephedrine and labetalol used during the surgical procedure (drugs used in response to haemodynamic instability), when deep neuromuscular block is used.

### a) Investigational Medicinal Product

The goal of the current study is to obtain additional data on two different anesthetic approaches, which includes drugs used according to their approved use and doses. By design, we will only obtain additional information on Sugammadex, with systematic collection and evaluation of adverse events for this drug. As such, the Investigational Product in this study is sugammadex.

The use of neostigmine in Group 1 fulfills criteria of a rescue medication. The remaining drugs are considered background medication, used according to approved and standard practice and no additional information will be collected concerning these drugs.

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All drugs, including sugammadex, will be used according to their approved and standard use at the trial site. Information concerning Sugammadex is contained in the attached Summary of Product Characteristics.

Sugammadex used for the trial will be supplied by MSD and will be relabeled and accounted for according to requirements for Investigational Medicinal Products.

The remaining drugs used during the trial will be supplied locally by CHP, according to standard procedures.

### b) Risks and benefits

The risks and benefits of Sugammadex are those described by the Summary of Product Characteristics:

The most commonly reported adverse reactions in surgical patients were anaesthetic complications.

Hypersensitivity reactions, including anaphylaxis, have occurred in some patients and volunteers (for information on volunteers, see Information on healthy volunteers below). In clinical trials of surgical patients these reactions were reported uncommonly and for post-marketing reports the frequency is unknown.

These reactions varied from isolated skin reactions to serious systemic reactions (i.e. anaphylaxis, anaphylactic shock) and have occurred in patients with no prior exposure to sugammadex.

Symptoms associated with these reactions can include: flushing, urticaria, erythematous rash, (severe) hypotension, tachycardia, swelling of tongue, swelling of pharynx, bronchospasm and pulmonary obstructive events. Severe hypersensitivity reactions can be fatal.

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### c) Treatment dose and schedule

35 patients randomized to group 2 will be administered a 4mg/kg dose to reverse the neuromuscular block at the end of the surgery.

### d) Rules and regulations

The study will be conducted according to ICH-GCP, the Declaration of Helsinki and all applicable laws and regulations, namely, but not limited to:

- Portuguese Clinical Research Law, 21/2014
- European Clinical Trials Directive 2001/20/EC
- European Directive concerning ICH-GCP 2005/28/EC
- Portuguese Data Privacy Law 67/98
- European Directive concerning data privacy 94/46/EC

### e) Study population

Seventy patients with an ASA score of I to III, 18 to 80 years old, scheduled for routine anterior cervical spine surgery in the Centro Hospitalar do Porto will be enrolled.

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## 5. Objectives

### a) Primary Objective

The primary objective of this study is to assess if the use of deep neuromuscular blockade reversed with sugammadex, and the consequent suppression of the EMG activity, can improve the overall stability of an anesthetic procedure (guided using BIS monitoring) and allow a reduction in the amount of anesthetic drugs required for adequate anesthesia.

The primary hypothesis is that there is a better anesthetic stability in the deep NMB group (Group 2) and that this is translated as a reduction of the BIS signal variability and a reduction in the required effect-site concentrations of propofol and remifentanil (representative of the total drug consumption).

### b) Secondary objectives

As a secondary objective, we will study the quality of recovery using the PQRS scale to see if maintaining a deep NMB level during surgery has an impact on the patients' quality of recovery.

The secondary hypothesis is that the quality of recovery (PQRS test) is better in the patients of Group 2.

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## 6. Study design

Patients subjected to anterior cervical spine surgery under general intravenous anesthesia will be randomized to receive one of two protocols regarding the neuromuscular blockade:

- Group 1 – Standard Clinical Practice Group - standard NMB, with a standard rocuronium dose for intubation (0.6 mg/kg). If required, the reversal of neuromuscular block is performed with neostigmine.
- Group 2 – Deep NMB group - with a standard rocuronium dose for intubation (0.6 mg/kg), followed by a constant infusion of rocuronium (10-15 μg/kg/min) to guarantee a PTC less or equal to 2 on the TOF monitor (PTC is evaluated every 5 minutes). The reversal of neuromuscular block is performed with Sugammadex (4 mg/kg).

### a) Primary Endpoints

- BIS signal variability using the measured standard deviation during the maintenance phase of anesthesia
- Required effect-site concentrations of remifentanil and propofol

### b) Secondary Endpoints

- PQRS results at 15 and 40 minutes after surgery (taking into account the patient baseline values of the PQRS test done on the pre-anesthetic visit)
- PQRS results at day 3 after surgery

### c) Study type

This is an interventional, phase 4, double-arm, parallel, randomized, open-label, single-center study aiming to compare two anesthesia protocols.

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### d) Study Timeline

- Study Start Date: April 2016
- Study End Date: April 2017
- First Patient In: April 2016
- Last Patient In: April 2017
- Last Patient Out: April 2017
- Study Analysis: May 2017
- Publication: November 2017

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### e) Flow-chart

| Assessment Title | Pre-anesthesia | Anesthesia procedure during surgery | 15 minutes PQRS Test | 40 minutes PQRS test | Follow-up |
|---|---|---|---|---|---|
| Assessment Number | Assessment 1 | Assessment 2 | Assessment 3 | Assessment 4 | Assessment 5 |
| Scheduled Day | One the day before surgery | Day 1, time 1 | Day 1, time 2: 15 minutes after surgery | Day 1, time 3: 40 minutes after surgery | 3 days after surgery |
| Scheduling Window | | >90 minutes | ±5 minutes | ±5 minutes | ±1 days |
| Informed Consent | X | | | | |
| PQRS test | X | | X | X | X |
| Medical History | X | | | | |
| Entry Criteria | X | X | | | |
| (Serious)Adverse Events | X | X | X | X | X |
| Physical Examination | X | | | | |
| Patient Data online recording | | X | | | |
| Patient randomization | | X | | | |
| Patient Satisfaction evaluation | | | | | X |
| Dispense Trial Medication | | X | | | |
| Pregnancy test | x | | | | |

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### f) Randomization and blinding procedures

This will be an interventional, randomized and unblinded study, performed at a single center (Centro Hospitalar do Porto).

Patient randomization will be done by a computer software programed with a varying block randomization technique (to ensure sample size due to the small number of patients in each group), using a uniform distribution. The software will be installed in the data collection computer, and the anesthesiologist will only know to which group the patient was randomly assigned before induction starts. Although block randomization is used, the computer software does not display information about the block assignment of future patients to the user. The software is programmed using the Statistical toolbox of MATLAB.

### g) Treatment

Trial participants will be randomly assigned (using varying block randomization) to one of two groups:

- Group 1 – Standard Clinical Practice Group - standard NMB, with a standard rocuronium dose for intubation (0.6 mg/kg). If required, the reversal of neuromuscular block is performed with neostigmine.
- Group 2 – Deep NMB group - with a standard rocuronium dose for intubation (0.6 mg/kg), followed by a constant infusion of rocuronium (10-15 μg/kg/min) to guarantee a PTC less or equal to 2 on the TOF monitor (PTC is evaluated every 5 minutes). The reversal of neuromuscular block is performed with Sugammadex (4 mg/kg).

General anesthesia will be performed with total intravenous technique using the hypnotic propofol, the analgesic remifentanil and the neuromuscular relaxant rocuronium. Target controlled infusion (TCI) will be used for propofol and remifentanil. Standard routine anesthesia practice for these procedures uses total intravenous anesthesia with propofol and remifentanil by TCI and rocuronium. A single bolus dose of rocuronium is given for tracheal intubation

and no further doses are administered during the procedure. At the end of surgery, NMB is reversed only if TOF is below 90%

### h) Treatment duration

Study treatment will be administered during surgery only, on day one.

### i) Discontinuation criteria

A patient may request to discontinue from the clinical trial at any time for any reason.

The investigator in any case in which emerging effects are of unacceptable risk to the individual subject, will discontinue the patient from the study. In addition, the investigator will to stop study for any patient with unmanageable factors that may interfere significantly with the trial procedures and/or the interpretation of results.

If the MAP does not respond to the protocol steps described in section 8, then the study should be stopped for that subject.

### j) Investigational product accountability

These requirements apply only to Sugammadex, which is already commercialized in Portugal and is used in current clinical practice at the Centro Hospitalar do Porto.

The internal labeling will be performed by our pharmacy department according to GCP guidelines and the local regulations for clinical trials. All drugs used, except for Sugammadex, will be labelled according to standard practice.

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The investigator will be responsible for the destruction of the supplies of Sugammadex at the study center pursuant to the GCP Guidelines, local regulations and the investigator's institutional policies.

Clinical supplies of the drug Sugammadex will be received by a designated person of the pharmacy department at the site, handled and stored safely and properly, and kept in a secured location. Clinical supplies are dispensed in accordance with the protocol, i.e. the pharmacy will be informed of the patient randomization and the need for the use of Sugammadex in the beginning of the surgery and the drug will be sent to the operating room.

The investigator will keep accurate records of the clinical supplies and the amount dispensed for each patient assigned to Group 2.

### k) Blinding and Un-blinding procedures

Not applicable.

### l) Source documents and data collection

Part of data will be recorded electronically: Trial participants will be monitored with standard ASA monitoring. Additional monitoring (i.e. intra-arterial pressure) will be provided depending on patient clinical status. The monitoring equipment is as follows:

- TOF Watch SX monitor for neuromuscular block assessment
- BIS – Bispectral Index Monitor (Covidien)
- Aisys Anaesthesia Monitor (General Electrics - GE)
- Fresenius Orchestra Base Primea, with TCI for propofol and remifentanil
- Syringe pump attached to the Fresenius Base Primea for the continuous infusion of rocuronium

Data collection software (Rugloop® Software and TOF Link) is installed on a Laptop computer connected to the Base Primea infusion pumps, the BIS monitor,

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GE monitor and TOF Watch monitor, allowing for all data to be recorded online. The patient data files generated by the Rugllop® software will be accessed using the Labgrab ® software and exported to excel files. TOF watch data will also be exported to excel files. All online data is posteriorly recorded in a patient individual CD.

All non-electronic data will be noted on the patients' paper CRF and on the RugLoop® software notes toolbar.

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## 7. Selection and discontinuation criteria

### a) Inclusion criteria

1. Patients ASA I-III
2. Between 18 – 80 years old
3. Scheduled for routine cervical surgery
4. Minimum duration of surgery is 90 minutes and performed with total intravenous anaesthesia (TIVA) with the hypnotic propofol, the analgesic remifentanil and the neuromuscular relaxant rocuronium
5. Patients that are able to and do provide a signed informed consent form

### b) Exclusion criteria

1. Patients with neuromuscular diseases and severe cardiac and respiratory pathologies
2. Contra indication for any of the drugs used
3. Not able to complete the baseline PQRS test.
4. Indication to perform tracheal intubation using fibroscopy
5. Patients who are pregnant or nursing

### c) Discontinuation criteria

A patient may request to discontinue from the clinical trial at any time for any reason.

The investigator in any case in which emerging effects are of unacceptable risk to the individual subject, will discontinue the patient from the study. In addition, the investigators will to stop study for any patient with unmanageable factors that may interfere significantly with the trial procedures and/or the interpretation of results.

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If the MAP does not respond to the protocol steps listed in section 8, then the study should be stopped.

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## 8. Treatment of study participants

### a) Informed Consent

Informed consent will be obtained by a medical investigator, part of the study team, during Assessment 1.

### b) Study procedures

Minimum duration of surgery is 90 minutes and general anesthesia will be performed with total intravenous technique using the hypnotic propofol, the analgesic remifentanil and the neuromuscular relaxant rocuronium. Target controlled infusion (TCI) will be used for propofol and remifentanil. Standard routine anesthesia practice for these procedures uses total intravenous anesthesia with propofol and remifentanil by TCI and rocuronium. A single bolus dose of rocuronium is given for tracheal intubation and no further doses are administered during the procedure. At the end of surgery, NMB is reversed only if TOF is below 90%.

#### i. Assessment 1

Assessment name: Pre-anesthesia

Timing: One the day before surgery

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| Informed Consent |
| PQRS test |
| Medical History |
| Pregnacy test |
| Entry Criteria |
| (Serious)Adverse Events |
| Physical Examination |

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| Patient Data online recording |
| Patient randomization |

The day before surgery informed consent will be obtained and baseline PQRS test performed. Patients with neuromuscular diseases and severe cardiac and respiratory pathologies, or that have any contra indication for any of the drugs used, or that are not able to complete the baseline PQRS test will be excluded from the study.

### i. Assessment 2

Assessment name: Anesthesia procedure during surgery

Timing: Day 1, time 1

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|---|
| Entry Criteria |
| (Serious)Adverse Events |
| Patient Data online recording |
| Patient randomization |
| Dispense Trial Medication |

On the day of surgery, the patients will be randomly assigned (using varying block randomization) to one of two groups:

- Group 1 – Standard Clinical Practice Group - standard NMB, with a standard rocuronium dose for intubation (0.6 mg/kg). If required, the reversal of neuromuscular block is performed with neostigmine.
- Group 2 – Deep NMB group - with a standard rocuronium dose for intubation (0.6 mg/kg), followed by a constant infusion of rocuronium (10-

15 μg/kg/min) to guarantee a PTC less or equal to 2 on the TOF monitor (PTC is evaluated every 5 minutes). The reversal of neuromuscular block is performed with Sugammadex (4 mg/kg).

The Hospital Pharmacy is informed of the need or not of Sugammadex and sends the drug to the surgery room (since the surgery will not take less than 90 minutes, there is plenty of time for the drug to reach the surgery room). The hospital pharmacy department already agreed with this procedure.

The anesthesia induction and maintenance is performed with the same protocol in both groups with TCI of propofol and remifentanil. During the procedure, the remifentanil and propofol effect-site target concentrations is titrated to achieve and maintain a BIS value between [40-60], and alarms are activated on the monitor; the Mean Arterial Pressure (MAP) should be maintained between [-30% +30%] of the baseline patient value.

Upon arrival at the surgery room, all patients will be monitored with standard ASA monitoring. Additional monitoring (i.e. intra-arterial pressure) will be provided depending on patient clinical status. The monitoring equipment is as follows:

- TOF Watch SX monitor for neuromuscular block assessment
- BIS – Bispectral Index Monitor (Covidien)
- Aisys Anaesthesia Monitor (General Electrics - GE)
- Fresenius Orchestra Base Primea, with TCI for propofol and remifentanil
- Syringe pump attached to the Fresenius Base Primea for the continuous infusion of rocuronium

## Anesthesia Protocol

The anesthesia protocol is as follows:

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- Baseline Mean arterial pressure is noted
- Induction is performed with target effect site concentration of remifentanil of 3 ng/ml and a constant 1% propofol infusion of 3,3 ml/kg/h until loss of consciousness
- Loss of consciousness is assessed using the standard method of loss of response to name calling and tapping on the forehead
- At loss of consciousness, the propofol effect-site concentration is noted and the TCI propofol target set to 25% of that concentration and then adjusted to maintain BIS between 40 and 60.
- TOF Watch monitor is calibrated according to manufactures instructions and the specifications of GCP of NMB monitoring [21]
- A bolus dose of rocuronium of 0.6 mg/kg is given, this dose is 2xED95 of rocuronium, to allow for tracheal intubation
- After tracheal intubation the muscle relaxant rocuronium administration protocol is performed according to the group the patient was assigned to (Group 1 or Group 2)
- During the procedure the remifentanil and propofol target concentrations are titrated to achieve and maintain a the BIS value between 40 and 60 (the BIS alarms are be activated in the monitor) and the Mean Arterial Pressure (MAP) between [-30% +30%] of the baseline

At the end of surgery the NBM reversal protocol is as follows:

- Group 1: Propofol infusion is stopped after the surgical dressing, if TOF<90 then neostigmine (40 μg/kg) plus atropine (20 μg/kg) are administered;
- Group 2: Propofol infusion is stopped after the surgical dressing and 4 mg/kg dose of Sugammadex is administered.

In both groups:

- time of recovery of consciousness is recorded
- time of extubation is recorded

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- the post-operatory analgesia is with iv paracetamol and iv parecoxib, and iv morphine if required

**Monitoring during surgery**

During the anesthesia procedure and for both groups of patients, the response protocols to BIS and MAP deviations from the target range are as follows:

Response Protocol to BIS values above 60:

- If EMG activity is present, the remifentanil effect-site target concentration is increased by steps of 1,5 ng/ml until a maximum of 15 ng/ml;
- If no EMG activity is present, the propofol effect-site target concentration is increased by steps of 0,5 μg/ml until the concentration required for loss of consciousness is achieved.

Response Protocol to Mean Arterial Pressure (MAP) values outside the target interval:

- If MAP is more than 30% below the baseline value, an ephedrine bolus of 5 mg is given every 3 minutes until the desired effect;
- If MAP is more than 30% above the baseline value, the remifentanil effect-site target concentration is increased by steps of 1,5 ng/ml until a maximum of 15 ng/ml is achieved. If the MAP value does not decrease to the desired range, then the propofol effect-site target concentration is increased by steps of 0,5 μg/ml until the value required for loss of consciousness is achieved;
- If the MAP still is outside the desired interval, then a 10 mg dose of Labetalol should be administer every 10 minutes until the desired effect.

If the MAP does not respond to the previous protocol steps, then the study should be stopped.

Additional rocuronium (muscle relaxant) bolus of 0.2 mg/kg are allowed in the following situations:

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- If during surgery, the surgeon mentions difficulties due to muscle contraction
- If the patient is showing spontaneous ventilation that prevents adaptation to mechanical ventilation

### i. Assessment 3

Assessment name: 15 minutes PQRS Test

Timing: Day 1, time 2: 15 minutes after surgery

| |
|---|
| PQRS test |
| (Serious) Adverse Events |

After the patient is moved from the surgery room to the recovery room, the PQRS test is performed in both groups at 15 minutes post-surgery. The PQRS tests are recorded in the patient's individual CRF forms.

### ii. Assessment 4

Assessment name: 40 minutes PQRS test

Timing: Day 1, time 3: 40 minutes after surgery

| |
|---|
| PQRS test |
| (Serious) Adverse Events |

The PQRS test is performed in both groups of patients at 40 minutes post-surgery.

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The main study finishes after the 40 minutes PQRS test is performed.

### iii. Assessment 5

Assessment name: Follow-up

Timing: 3 days after surgery

| |
|---|
| (Serious) Adverse Events |
| Patient Satisfaction evaluation |

At the 3rd day after surgery a telephone contact is made to identify the occurrence of any Adverse Event (AE) (according to Good Clinical Practice (GCP) guidelines and pharmacovigilance directives), as well as to evaluate patient satisfaction using only the PQRS questions that address this issue. If at the 3rd day after surgery the patient is still in the hospital, than the contact is performed face to face by the investigator or designated researcher. The overall data acquisition for each patient ends at this point.

The occurrence of SAE and AE is noted on the specific forms on the patient individual CRF and acted accordingly to the GPC guidelines.

The individual patient data will be anonymized after the 3rd day contact.

### iv. Discontinuation Visit

| |
|---|
| (Serious) Adverse Events |
| Patient Satisfaction evaluation |

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### c) Compliance with study treatment

Protocol compliance will be monitored, including accurate prescription and administration of study treatment according to protocol.

Study treatment (IMP and NIMP) will be supplied and administered by medical personnel, so no compliance issues are expected to occur.

### d) Concomitant and prohibited medication

Allowed concomitant medication and prohibited medication are those described by the SoPC of the IMP and NIMPs.

### e) Expenses and benefits

Participants in the study are not expected to have additional expenses due to their study participation, since treatment and follow-up are similar to standard practice. Participants may benefit from the close monitoring due to study design.

Unscheduled visits travel expenses (until 3 days after discharge) will be reimbursed by the Sponsor (up to € 30) against expenditure presentation document).

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## 9. Efficacy evaluation

### a) Efficacy measure

A 25% reduction on the BIS variability (standard deviation) is considered clinically relevant.

### b) Methods

All hemodynamic and brain monitoring, TOF monitoring, and infusion pumps data will be recorded online during surgery with a sample time of 5 seconds, using data collection software on a laptop connected to all monitors and infusion pumps.

Data collection software (Rugloop® Software and TOF Link) are installed on a Laptop computer connected to the Base Primea infusion pumps, the BIS monitor, GE monitor and TOF Watch monitor, allowing for all data to be recorded online. The patient data files generated by the Rugllop® software will be accessed using the Labgrab ® software and exported to excel files. TOF watch data will also be exported to excel files. All online data is posteriorly recorded in a patient individual CD. All non-electronic data will be noted on the patients' paper CRF and on the RugLoop® software notes toolbar.

The total doses of ephedrine and labetalol are used as a surrogate variable, since they are the drugs used in the response protocol to hemodynamic instability (MAP being outside the desired target range).

The following recorded data will be analyzed per patient and compared between the two study groups:

- BIS signal variability using the measured Standard deviation during the maintenance phase of anesthesia
- BIS average value during the maintenance phase of anesthesia
- Duration of periods of BIS values above 60 and below 40
- Average effect-site concentrations of propofol and remifentanil required during the maintenance of anesthesia
- Total doses of remifentanil, propofol, ephedrine and labetalol

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- PQRS results at 15 and 40 minutes after surgery (taking into account the patient baseline values of the PQRS test done on the pre-anesthetic visit)
- Patient satisfaction evaluated using the specific PQRS questions

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## 10. Safety evaluation

Each patient is considered to have ended participation in the study when he/she has completed the last telephone contact at 3 days post-surgery to verify the occurrence of any adverse events (AE) according to the phamacovigilance guidelines, or prematurely discontinues from the trial.

Each patient will be monitored for the occurrence of AEs immediately after the subject has signed informed consent through 3 days after the patient has done the last PQRS test (at 40 minutes after surgery). The patient will be monitored by the investigator or assigned researcher at hospital discharge (usually 24-48 hours after surgery) and then at the 3rd day after surgery (by telephone call) to monitor occurrence of AEs. If at the 3rd day after surgery the patient is still in the hospital, then the investigator or designated researcher will talk personally to the patient.

Follow-up procedures related to the occurrence of Serious Adverse Events (SAE) may continue beyond the end of the clinical trial.

The CRF of the patient will have the AE and SAE forms according to GCP guidelines and local regulations.

### a) Definitions and reporting

For the purpose of this Protocol the below terms shall be defined as follows:

#### Adverse Event (AE)

"Adverse Event" or "AE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug.

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### Serious Adverse Event (SAE)

"Serious Adverse Event" or "SAE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug that results in death, a life-threatening drug experience, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, cancer, or is a new cancer if the cancer is the condition of the study, or overdose. Other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed previously should also be considered "serious".

### Suspected Unexpected Serious Adverse Reaction (SUSAR)

"Suspected Unexpected Serious Adverse Reaction" or "SUSAR" shall mean any Serious Adverse Event, the nature, severity or frequency of which is not consistent with information in the most current investigator's brochure, or with respect to a marketed product the most current Summary of Product Characteristics or Package Insert.

### Drug Exposure during pregnancy or lactation

All reports of Study Drug exposure during pregnancy or lactation (including a female partner of a male Study subject using the Study Drug), whether associated with an AE or not, will be reported to INFARMED and CEIC will be notified in accordance with the timelines and contact information for an SAE. Principal Investigator will follow pregnancies to term to obtain the outcome of the pregnancy. The outcome of the pregnancy will be forwarded to INFARMED and CEIC. Sponsor will also forward these reports to MSD that is the supplier of the Study Drug.

### Event of Clinical Interest (ECI)

An "Event of Clinical Interest" is a non-serious adverse event or occurrence that is designated to be of special interest and must be reported to the sponsor as

though it were a serious adverse event. The following events are considered events of clinical interest for this trial:

1. An overdose of Sponsor's products that is not associated with clinical symptoms or abnormal laboratory results is to be reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

2. An elevated AST or ALT lab value that is ≥3 x the upper limit of normal (ULN) and an elevated total bilirubin lab value that is ≥2 x ULN and, at the same time, an alkaline phosphatase lab value that <2 x ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing is to be reported as a non-serious ECI. Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

3. Events of hypersensitivity: serious adverse events suggestive of hypersensitivity and/or possible events of anaphylaxis will be considered events of clinical interest. In case of hypersensitivity, additionally to the CIOMS the reporting investigator will also fill in from 211-PV031 (provided in attachment) and submit it within the same timelines as indicated above.

## Overdose

In this current trial, an overdose of sugammadex is considered a dose greater than the maximum dose recommendation of sugammadex (i.e., any dose greater than 16 mg/kg). In previously-conducted clinical trials, there was one case of an accidental overdose with 40.0 mg/kg reported without significant undesirable effects. In a human tolerance study, sugammadex was tolerated well in doses up to 96.0 mg/kg. Please refer to the SPC for further information.

## Product Quality Complaint

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A product quality complaint (PQC) is any written, electronic or oral communication that alleges a product defect. A PQC includes suspected product counterfeit, diversion or tampering. A PQC does not include Product Complaints alleging an AE.

## Planned Hospitalization

A hospitalization planned by the subject prior to signing the informed consent form is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete.

However, if the event/condition worsens during the trial, it must be reported as an AE or SAE.

## Medication Error

A medication error is any preventable event that may cause or lead to inappropriate medication use, including unintended accidental exposure or subject or patient harm while the medication is in the control of a health care professional, subject or patient, or consumer. Such events may be related to professional practice, clinical trials, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature; compounding, dispensing, distribution, administration, education, monitoring, and use.

## Potential Medication Error

A potential medication error is an individual case safety report of information or complaint about product name, labeling, or packaging similarities that does not involve a subject or patient (eg, if a subject reports that one of the investigational

products looks like a different product, the report would be considered a potential medication error).

### Trial Procedure Related Events

A clinical trial procedure related event is an AE that could be associated with the trial procedures, rather than the investigational product or its administration.

Trial procedures include all treatment procedures and medical procedures for physical examinations, medical investigations, and laboratory assessments or other activities specified in the protocol for the purpose of the clinical trial.

## b) Reporting

### SAE and SUSAR Reporting

- SAE and SUSAR reports and any other relevant safety information will be forwarded by the Principal Investigator to the following CHP e-mail: ensaiosclinicos.farmacia@chporto.min-saude.pt.
- Sponsor will forward to INFARMED and CEIC, any SAE and SUSAR information, including, but not limited to, all initial and follow-up information involving any Study subject in the Study.
- Notification will be made in the form of a completed CIOMS I within one (1) business days of learning of the SAE or SUSAR.
- All SAE and SUSAR information will be transmitted in the English language and contains the reporter's name and the Study subject identifier code.
- SUSAR information will be reported unblinded.
- Randomization codes for all other SAEs will be provided to INFARMED at end of Study.
- The reporting investigator will provide a causality assessment for all reported SAEs.
- Sponsor will ensure timely reporting of SUSAR to the relevant competent authorities.
- As supplier of the drug under study, MSD will be informed on SAE and SUSAR by the Sponsor to the following e-mail:

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pharmacovigilance.portugal@merck.com, or by Fax: +351 214 465 799, preferably on the same day competent authorities will be notified.

- By timely it is meant that SUSAR concerning death of a subject or life-threatening situations will be submitted within 7 calendar days after such a case is known by an investigator of this study, and within 15 calendar days for all other SUSAR.

### DSUR Reporting

Sponsor will remain responsible for redacting and submitting to all relevant parties the Development Safety Update Reports (DSUR) according to the applicable legislation. The Sponsor also will forward the final DSUR to the Competent Authorities and to MSD.

### Product Quality Complaint Reporting

In the event Sponsor will become aware of a defect or possible defect in the Study Drug, Sponsor will notify INFARMED and MSD within one business day of first becoming aware of the possible defect.

### Other Information

MSD may will provide the Sponsor/Principal Investigators, at Study initiation and on an ongoing basis, with information regarding the Study Drug, including but not limited to safety information. The Sponsor and Principal Investigator agree to hold this information in confidence.

## c) Safety Monitoring

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### Monitoring Adverse Events

Subjects will be monitored for the occurrence of SAEs immediately after the subject has signed informed consent. Subjects enrolled in the study will be monitored for both AEs and SAEs.

Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator.

AEs, actions taken as a result of AEs, and follow-up results must be recorded in the CRF, as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the trial and SAEs, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate until final resolution or stabilization of the event(s).

### Monitoring Laboratory Assessments

Assessments of laboratory parameters will be performed locally. These laboratory values will be reported to the investigator by the laboratory and the investigator will review them for significance and consideration as an AE.

## d) Assessment of Adverse Events

### Assessment of Severity

Where the determination of AE severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of a medically-qualified investigator.

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The severity of AEs will be graded according to the following definitions:

**Mild:** awareness of sign, symptom, or event, but easily tolerated;

**Moderate:** discomfort enough to cause interference with usual activity and may warrant intervention;

**Severe:** incapacitating with inability to do normal daily living activities or significantly affects clinical status, and warrants intervention;

## Assessment of Causality

A medically qualified investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, as unlikely related, possibly related, or probably related, based on available information, using the guidelines listed below:

**Unlikely related:** no temporal association, or the cause of the event has been identified and attributed to other disease or drug; or the drug, biologic, or device cannot be implicated based on available information;

**Possibly related:** temporal association, but other etiologies are likely to be the cause; however, involvement of the drug, biologic, or device cannot be excluded based on available information;

**Probably related:** temporal association, other etiologies are possible, but unlikely based on available information.

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## 11. Statistics

### a) Methods

Differences in age, weight, and height between the groups will be analyzed with t-test.

Continuous data will be analyzed using independent samples t test, or RM ANOVA for repeated measurements.

Univariate analyses will be conducted using chi-square analysis or Fisher exact test where appropriate, to analysis de PQRS recovery result at discrete time points, and repeated measures ANCOVA for continuous data.

Statistical analysis of the subcategories of the PQRS test will be performed using the Cochran Mantel – Haenszel test on the proportions of recovery for each group with continuity correction over two measurement periods.

### b) Number of participants

Sample size calculation with a power of 0.80 and an $\alpha$ of 0.05, considering the primary hypothesis of a reduction in the BIS variability (measured as the standard deviation) and a reduction in the propofol and remifentanil drug consumption (measured as the average effect-site concentration required) during maintenance of anesthesia.

To estimate the standard deviation of our population, we searched our database for standard clinical practice cases with: online data recording; cervical spine surgery; BIS average values within the recommended target values [40-60]; TCI anesthesia with propofol and remifentanil.

A total of 12 patients data were analyzed (mainly due to the lack of online recording during the procedures), the average BIS standard deviation was 8.7±3.14, and the average propofol and remifentanil effect-site concentrations were 2.68±0.9 μg/ml and 2.83±0.8 ng/ml, respectively.

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A 25% reduction on the BIS variability (standard deviation) was considered clinically relevant, and gave a minimum sample size of 26 per group.

A reduction on propofol average effect-site concentration of 20% was considered clinically relevant, and gave a minimum sample size of 34 per group.

A reduction on remifentanil average effect-site concentration of 20% was considered clinically relevant, and gave a minimum sample size of 24 per group.

Considering the above results and the possibility of patient exclusion due to external complications during surgery, a total of 35 patients per group will be included in the study.

The secondary variable, result of the PQRS test was not used in the sample size calculation, since there are no studies on the comparison of recovery after two different interventions and the data regarding sample calculation that the authors of PQRS showed us are for the recovery at 3 days post-surgery, which is not comparable to our study. Therefore we did not considere adequate to estimate a percentage difference for which we do not know the clinical reality.

The surrogate variables, consumption of ephedrine and labetalol will be analyzed since these drugs are used in the response protocol to target deviations, but they are not considered for the sample size calculation.

### c) Level of statistical significance

The sample was calculated at a significance level of 95%. A p-value below 0.05 is considered statistically significant.

### d) Study termination

Data analysis is planned for the end of the trial. No early study termination is planned.

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### e) Missing data

Participants with missing primary endpoint data will not be included in the analysis.

### f) Deviations

Any change to the statistical plan will be submitted to the competent authorities prior to its implementation.

### g) Inclusion in analysis

All data will be included for the analysis (Intention to treat).

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## 12. Direct access to source documents

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to authorized individuals, as the clinical trial monitors, auditors or health authority inspections. The objective of these accesses is to ensure the trial is being conducted according to local laws and regulations and ICH-GCP.

All site facilities related to the study conduct can be visited during an audit (e.g. pharmacy, laboratory, archives).

The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any monitoring or auditing activity.

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## 13. Quality control and quality assurance

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

### Inspections and Audits

The Principal Investigator will notify the Administration of CHP within twenty-four (24) hours in the event that any regulatory authority notifies the Study site of a pending inspection/audit that concerns the Study or Institution's ability to perform clinical research. In addition, Principal Investigator will forward to Administration of CHP any written communication received as a result of the inspection/audit within twenty-four (24) hours of receipt of such communication and allows CHP to assist in responding to any citations involving the Study Drug. Such responses shall be made as soon as possible under the circumstances or within any earlier deadline set by the issuing regulatory authority. Principal Investigator also will provide to Administration of CHP copies of any documents provided to any inspector or auditor. In the event the regulatory authority requests or requires any action to be taken to address any citations, Principal Investigator and Administration of CHP agree to take such action as necessary to address such citations.

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## 14. Ethics

Written informed consent will be obtained from all patients. Research will be carried out in compliance with the Declaration of Helsinki.

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice E6.

### a) Responsible ethics committee

The study will be submitted to the Portuguese Central Ethics Committee CEIC and only start recruitment after receiving its positive opinion.

### b) Regulatory Approval

The study will be submitted to the Portuguese Regulatory Authority INFARMED and only start recruitment after receiving its approval.

### c) Patient Confidentiality

The study will be submitted to the Portuguese Data Privacy Agency CNPD and only start recruitment after receiving its approval for data collection.

The trial staff will ensure that the participants' anonymity will be maintained. The participants will be identified within the trial by a numeric code. The numeric code correspondence to the participant can only made at the investigative site here that participant is being followed.

Trial data will be recorded only by authorized trial personnel. Trial data will only be accessed by authorized personnel.

Patients' data during surgery will be recorded on a research laptop with a code generator, which protects patient anonymity by generating a code for each individual patient.

All paper records (CRF) with the PQRS test results at the different time points will use the designated individual patient code. The patient CRF's will be kept on a secure archive cabinet during the duration of the study. The electronic data files

will be kept on the research laptop (with restricted permissions) and each patient will also have its own individual data CD.

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## 15. Data handling record keeping

Clinical trial data will be maintained in the Case Report Form developed for the trial. All hemodynamic and brain monitoring, TOF monitoring, and infusion pumps data will be recorded on the hospitals computers. PQRS paper questionnaires will be filled out by the trial participants and kept in the participant's clinical chart.

Remaining source documentation is to be maintained as part of the participant's clinical chart. Deviations from this documentation method will be documented.

All data are to be attributable, legible, contemporaneous, original and accurate.

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## 16. Financing and insurance

The study received a grant from Merck Sharp & Dohme and IMP (sugammadex) will be supplied by Merck Sharp & Dohme.

The study was designed and will be conducted, analyzed and interpreted by the investigator according to publications policy.

A clinical trial insurance for the trial participants and the investigators will be contracted by the study Sponsor.

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## 17. Publication policy

All study data and results are owned by the Investigator/Sponsor. Only the principal investigator and the research team will have access to all research data and results during the study. Investigator/Sponsor agree however that the final results generated during the study may be used by MSD for any scientific or business purpose. In the addition to the publication process Sponsor/Principal Investigator shall only use the research data and results generated during the course of the study for internal, non-commercial teaching and research purposes. Sponsor/Investigator agree not to provide any commercial third party with access to or with the right to use the data or results for any purpose without the written permission of MSD.

Principal Investigator has the right to publish or publicly present the results of the Study and MSD shall have the right to review and comment on any Public Presentation. For this purpose, the Principal Investigator shall provide 45 days, written notice to MSD prior to submission for publication or presentation to permit MSD to review drafts of abstracts and manuscripts for publication which report any results arising out of the study. Such 45 days notice period shall not commence until MSD has received all the relevant data associated with the public presentation in order for MSD to properly review and comment on the public presentation.

If the parties disagree concerning the accuracy and appropriateness of the data analysis and presentation, and/or confidentiality of MSD's Confidential Information, Sponsor/Principal Investigator agree to meet MSD's representatives at the clinical study site or as otherwise agreed, prior to submission of a public presentation, for the purpose of making good faith efforts to discuss and resolve any such issues or disagreements. Principal Investigator agrees to acknowledge MSD in any public Presentation using the following language: "Supported in part by a research grant from Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp."

In making a public presentation, Sponsor/Principal Investigator shall comply with all laws, regulations and accepted guidelines of peer reviewed medical journals

and any specific guidelines established by congress and/or journals to which the public presentation will be submitted. Sponsor/Principal Investigator represent that designated authors and contributors shall meet the minimum requirements of International Committee of Medical Journals Editors.

The Principal Investigator anticipate to write two papers. One focusing on the primary objective of the study and the other on the secondary objective.

The journals at which Principal Investigator intend to submit are Anesthesia & Analgesia and the British Journal of Anaesthesia.

The Principal Investigator also anticipate to submit two abstracts. The scientific meetings that he is considering are the EuroAnaesthesia 2018 and the American Society of Anesthesiologists Annual Meeting (ASA) 2017.

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## 18. Appendix

- PQRS Physician Quality Reporting System
- Summary of Product Characteristics Sugammadex, last updated on 25-Jul-2013

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